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1929 (13) breast milk

1. hunger oedema (14) human milk
2. hepatic structures
3. emotional disturbances
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5. Renal function
6. water metabolism
7. antigenic stimuli
8. serum cholinesterase
9. cardiac output (10) heart
11. unlimited foods (2) lactation

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MEDICAL RESEARCH COUNCIL

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No. 275

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BY

MEMBERS OF THE DEPARTMENT OF EXPERIMENTAL MEDICINE, CAMBRIDGE, AND ASSOCIATED WORKERS

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LIST OF AUTHORS

Professor R. A. McCance, M.D., Ph.D., F.R.C.P., F.R.S., Department of Experimental Medicine, Cambridge.
Miss E. M. Widdowson, D.Sc., Department of Experimental Medicine, Cambridge.
R. F. A. Dean, M.R.C.S., L.R.C.P., Department of Experimental Medicine, Cambridge.
Miss L. A. Thrussell, S.R.N., Department of Experimental Medicine, Cambridge.

A. M. Barrett, M.B., Department of Pathology, Cambridge.
F. R. Berridge, M.B., D.M.R., Department of Experimental Medicine, Cambridge.
D. Russell Davis, M.D., M.R.C.P., D.P.M., Department of Experimental Psychology, Cambridge.
P. G. H. Gell, M.B., Department of Pathology, University of Birmingham.
E. M. Glaser, M.C., M.D. (Bratislava), Ph.D., Department of Experimental Medicine, Cambridge.
Mrs. M. H. D. Gunther, M.D., University College Hospital, London, W.C. 1.
Miss S. M. Howarth, M.B., B.S., National Heart Hospital, London, W. 1.
Miss A. O. Hutchinson, Ph.D., Department of Experimental Medicine, Cambridge.
P. E. H. Jones, B.Sc., M.R.C.S., Department of Experimental Medicine, Cambridge.
R. A. Kekwick, D.Sc., Lister Institute of Preventive Medicine, London, S.W. 1.
M. D. Newman, M.B., Department of Experimental Medicine, Cambridge.
Miss K. M. Prior, M.S.R., Department of Experimental Medicine, Cambridge.
Miss S. P. V. Sherlock, M.D., M.R.C.P., British Postgraduate Medical School, Hammersmith, W. 12.
Miss J. E. Stanier, D.Phil., Department of Biochemistry, Oxford.
P. R. V. Tomson, M.B., Department of Experimental Medicine, Cambridge.
Miss V. M. Walshe (Mrs. I. D. P. Wootton), Ph.D., British Postgraduate Medical School, Hammersmith, W. 12.

PREFACE

BETWEEN 1919 and 1922 the Medical Research Council and the Lister Institute of Preventive Medicine maintained in Vienna a small team of British scientists engaged in the study of the deficiency diseases then prevalent in that part of Europe. The valuable results which Dame Harriette Chick and her colleagues achieved, and the esteem in which they were held by the Viennese physicians among whom they worked, were a source of encouragement to the Council when twenty years later it became necessary to prepare for similar work at the end of a second world war. As early as July, 1943, the Council's Accessory Food Factors Committee made a start by appointing a subcommittee, which drew up a list of the scientific problems most needing study and of the workers likely to be available for the purpose. In several of the allied countries undernutrition was known to be widespread and the situation in each of them was carefully surveyed but, as long as the war continued, the presence of the armies, the requirements of troop movements, and the absence of quiet hospital and laboratory facilities made them seem unpromising places in which to establish a semi-permanent Unit. Observers sent to Holland and a small team which made a flying visit to Belsen Concentration Camp gave valuable help with relief work, but the war came to an end without any major research expedition having set out.

Towards the close of 1945, however, reports of the nutritional position in Germany itself began to come in and it was decided to send Dr. McCance and Dr. Widdowson to make a survey of the research possibilities there. Accompanied by Squadron-Leader Smart, kindly seconded by the Royal Air Force, they set out in March, 1946, and on their recommendation the Council established a Unit at Wuppertal in the following June. The enterprise was made possible by the goodwill and co-operation of the Control Commission for Germany, which arranged for the housing, food and transport of the Unit, and the Council would like to take this opportunity to acknowledge with gratitude the assistance accorded to the Unit throughout its stay in Germany by Brigadier W. Strelley-Martin, Dr. J. G. Gill and all the other members of the Control Commission.

The headquarters of the Unit were set up in the research laboratories of the I.G. Farbenindustrie, Wuppertal-Elberfeld, which were undamaged and excellently equipped. Three small wards were placed at its disposal in the Municipal Hospital, Wuppertal-Barmen, and an out-patient clinic was held in the same hospital twice a week for two years; facilities at other institutions were made available as need arose.

The object of the expedition was to study the effects of undernutrition on the physical and moral well-being of a modern community, but no attempt was made to survey the entire population of Wuppertal and the investigation was deliberately concentrated on representative individuals and small groups. Until the general level of nutrition improved these were drawn predominantly from members of the civilian population but by the beginning of 1948 the Unit was largely occupied in studying the prisoners of war who were being repatriated from Russia. Moderate undernutrition was widespread among both these classes but the last stages of starvation, so common in the concentration camps, were never encountered by members of the Unit in the course of their work in Germany. The findings described in this Report, therefore, do not necessarily apply to the most advanced degrees of undernutrition.

The shortage of food in German towns just after the war was shown to have a small but measurable effect on the size of newborn babies, and the breast milk of mothers who were not obtaining enough to eat was found to be reduced in amount, although its composition remained unchanged. The history and aetiology of hunger oedema were studied and the swelling of the ankles and legs, so much discussed in recent times, was found to be a relatively unimportant part of the total water metabolism of the undernourished person; the essential change was a loss of fat and of cellular tissue and an increase in the volume of the extracellular fluids of the body. No vitamin or mineral deficiencies were found in Wuppertal, although lesions of the skin which appeared to be the same as those attributed to vitamin deficiencies in other parts of the world were observed.

In every investigation normal people were studied side by side with the undernourished, a procedure that has often been neglected although the principle is important in all biological work. The constant use of these "controls" proved that it is much more difficult to find departures from the normal in those who are undernourished than has hitherto been supposed.

Although the Unit was staffed mainly from the Department of Experimental Medicine, Cambridge, more than forty of the Council's staff, as well as workers from other laboratories and hospitals, came to Wuppertal at one time or another, a few as visitors, the rest to conduct special researches or to help with those already under way. The Report reflects this policy to some extent, in that it consists of a series of papers, each contributed by the author or authors responsible for studying a particular aspect of undernutrition.

It is pleasant to be able to record that in the course of the investigations a spirit of friendly co-operation and mutual assistance grew up between the members of the Unit and their German colleagues. This collaboration undoubtedly contributed materially to the success of the various investigations.

The Unit returned to England in January, 1949.

MEDICAL RESEARCH COUNCIL,
38 Old Queen Street,
Westminster, London, S.W.1

April 16, 1951

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STUDIES OF UNDERNUTRITION, WUPPERTAL 1946–9

I. THE GERMAN BACKGROUND

by R. A. McCance and E. M. Widdowson

THE TOWN AND PEOPLE OF WUPPERTAL

Wuppertal lies in the valley of the river Wupper and in 1939 was a wealthy industrial and residential area. It was essentially a fusion of two larger towns, Elberfeld and Barmen, and of two smaller ones, Vohwinkel and Oberbarmen. The population of Wuppertal as so constituted was about 500,000, and there were a number of smaller towns, such as Ronsdorf and Neviges, each with its own industrial plant, served by the Wuppertal tramway system. The town of Wuppertal itself was long and narrow, and did not reach as far as the tops of the hills flanking the river Wupper. These tops were mostly wooded and very beautiful (Plate I). Twenty miles to the north lay Essen and the string of Ruhr towns stretching east and west. Hagen was the next town on the east side; Solingen, the steel centre, and Köln lay 12 and 30 miles respectively towards the south-west, and Remscheid to the south. Between these towns the country was entirely agricultural or wooded, and suburban houses did not spread out into the country as they do in England. The townspeople lived in blocks of flats, and few of them had gardens (Plate II).

Wuppertal derived its fame and wealth from the textile industry, particularly lace, ribbons, and elastics. The factories were mostly small and privately owned. The Bayer pharmaceutical works, however, which became part of the I.G. Farbenindustrie in the middle 1920's, lay in Elberfeld, and the I.G. pursued the policy of developing a large pharmaceutical research centre there. The firm had always been very prosperous and the workmen changed little from year to year.

The inhabitants of Wuppertal were partly Protestant, partly Roman Catholic. They were probably very similar in most respects to the inhabitants of many other prosperous German towns. They lived well and did not take a great deal of exercise. Consequently their weight was a serious preoccupation to many of them. The wealthy houses had balances in the bathrooms, and nearly every inhabitant of Wuppertal could with confidence give a figure for his weight and its annual excursions when times were good.

The hospital services must have been excellent before the war. There was a large municipal hospital in Barmen and another in Elberfeld, and a number of other smaller hospitals run by religious institutions and other bodies. The largest and best of these was built not long before the war and was taken over by the British as the 77th General Hospital when they occupied the town. There was also a large hospital for women.

Wuppertal was not raided seriously till 1943. On the night of May 30 there was a very heavy incendiary raid by the R.A.F., as a result of which much of Barmen was burned to the ground. About a month later, on the night of June 26, the R.A.F. returned and destroyed a large part of Elberfeld by the same technique. On November 11, 1944, there was a small daylight raid on Oberbarmen with high explosive, and during the winter of 1944–5 there were several sporadic raids on parts of the built-up area which were still standing. On March 13, 1945, a very heavy raid with high explosive in the middle of the afternoon completed

the destruction of Oberbarmen. There was only one more bomb raid, a small one, on March 19, 1945. The northern fringes of the townships escaped serious damage, and so did the western end of Elberfeld and Vohwinkel. The municipal hospital in Barmen, the women's hospital and the new hospital (which was to become the British 77th General) were all on the northern slopes of the valley and were left intact. The municipal hospital in Elberfeld was not so fortunately placed and was partly destroyed. The Bayer (I.G. Farben) works escaped all structural damage. These raids caused gigantic loss of property and produced intense overcrowding (Plate III). Hundreds of families lost everything they possessed and found themselves beholden to their friends or the Town Council for clothes, food, and shelter. Their losses, grievous enough at the time, often had far-reaching effects, for many German housewives had prepared themselves for a food shortage by laying aside stores of tinned food and other non-perishable commodities, and these were completely destroyed. Furthermore, when food did become scarce in 1946, people who had lost everything had no means of barter and could not, therefore, supplement their official rations by exchange (see later).

The demand for dwelling space was partially satisfied in three or four ways. Empty houses and even rooms were requisitioned, families were given accommodation under the roofs of friends or relatives, and every available cellar or attic was turned into a dwelling. The iron pipes which could be seen sticking out of the heaps of ruins all over Germany generally indicated a fire and habitation in the cellar beneath (Plate IV). Very small prefabricated wooden hutments were put up in gardens in the town and in colonies on the slopes of the surrounding valleys. Later, the erection of more permanent dwellings, made of bricks salvaged from the ruins, was begun amid the destruction and outside the town. These mostly appeared to have been built by free enterprise, and they presented a very variable standard of architectural skill (Plate V). Finally, the "Bunkers" were pressed into service as dwellings. These massive structures had been built as air-raid shelters. Some of them were many stories high, some were completely underground. All were built on the same plan with ferro-concrete walls many feet thick and without windows (Plate VI). Ventilation was effected by fans and pipes, and each floor was served by corridors off which opened small rooms resembling ships' cabins. Lavatory and cooking accommodation were provided on each floor, and each "cabin" was equipped with two or four bunks in double tiers. A family was assigned one or perhaps two cabins. It must be stated in all fairness that these "Bunkers" were exceedingly well constructed. A smell of cooking always pervaded them, however, and the everlasting artificial light must have been very trying, but they were, on the whole, well lit and had adequate ventilation. One of the "Bunkers" in Wuppertal, used as transit accommodation for refugees, was built on a rather different principle and contained large dormitories.

GERMAN RATIONS AND FOOD SUPPLIES

The Normal Consumer

We made a few investigations in Hamburg in April, 1946, during our preliminary survey of the British Zone, and the Unit began to work in Wuppertal in the middle of June. At this time all foods were rationed. The official rations provided 1,052 Calories per day for the normal consumer, and had done so for three months. Table I shows how the rations were made up and Plate VII the people's views about them.

TABLE 1

Ration scale for normal consumers in June, 1946

Food	Quantity per 4-week period (g.)	Calories/day
Bread	7,000	588
"Nährmittel" ..	1,000	117
Meat	420	31
Fish	900	44
Butter	325	86
Margarine ..	75	20
Sugar	500	71
Jam	450	36
Cheese	62·5	5
Skim milk ..	3,500	43
Artificial coffee	125	—
Vegetables ..	2,000	11
		1,052

The bread, usually dark brown in colour, was not made from wheat only, for rye, oats, barley, and maize were included in the flour at different times in variable amounts. In milling the wheat all the bran and germ went into the flour used for baking bread, but some of the semolina was excluded. Thus, according to the ordinary designation, the flour was of an extraction rate higher than 100 per cent. It was not generally fortified with calcium.

Oatmeal, macaroni, semolina and other cereals were included under the heading "Nährmittel". They were very popular for thickening soups, but could not always be obtained. From September, 1946, onwards they were not available for many months, and no other food was issued instead, so although Nährmittel always appeared on paper as part of the ration, they must be discounted in any consideration of the actual food intakes at that time.

One-quarter of the meat ration was reckoned to consist of bone, and if a piece of boneless meat was bought only 75 per cent of the weight would be supplied and a piece of bone would be added to make up the remaining 25 per cent. The ration of 900 g. of fish per four-weekly period consisted chiefly of herrings, which were usually eaten salted and pickled under the name of "Salzheringe". If other fish with a lower Calorie value was on sale, a correspondingly larger weight was allowed.

The jam was of very poor quality, made from vegetables and sugar with artificial fruit flavourings. Treacle was occasionally issued instead. The cheese was always a low-fat variety. "Quark", a kind of milk cheese, could sometimes be bought instead, in which case twice the weight of the normal ration was allowed since this product was reckoned to have half the Calorie value of real cheese. Skim milk appeared on the ration scale, but it was not always available, and when it was it was sometimes sour. Few people were able to obtain more than half their ration. The artificial coffee was made from roasted cereals.

No new potatoes were on sale to the normal consumer in 1946 until the end of July, and none of the previous year's crop had been available for many months past. People who had gardens and who had managed to lay in a stock of potatoes

received 2,000 g. less bread during the June–July rationing period. The vegetables consisted during the spring and early summer chiefly of "Steckrüben", a coarse type of swede turnip, and of white cabbage. As the new season's vegetables began to come in, the variety available naturally improved.

In the next rationing period (July 22–August 18) the Calories were theoretically increased to 1,137 a day, because 8,000 g. of potatoes were included in the four weeks' ration. These were, however, rarely on the market, and few were fortunate enough to obtain them. The meat ration was increased to 450 g., and the fish decreased to 600 g. Butter was reduced to 125 g. and sugar to 250 g. Other items remained the same. This reduction in fat was considered by the German people to be one of the greatest hardships they had had to face, and they never ceased to bemoan the fact that the shortage of fat was undermining their health.

With the beginning of the 92nd rationing period (August 19–September 15) a new system was introduced. The Calorie allowance for the normal consumer still remained at 1,137, but dwellers in large cities, among which Wuppertal was included, were entitled to a supplement of 200 Calories a day. This was made up from an additional 1,600 g. of bread, 400 g. of meat, and 140 g. of butter during the four-week period. In September and October the meat and butter returned to their old levels (450 g. and 125 g. respectively), but the bread ration was further increased, so that city dwellers were entitled to 9,900 g. during this rationing period. Their official Calorie allowance was then reckoned to be 1,409 a day.

In the middle of October the ration for all normal adult consumers was increased to 1,550 Calories a day, irrespective of where they lived. The bread allowance was raised to 10,000 g. per four weeks, Nährmittel to 1,750 g., meat to 500 g., and sugar to 750 g., while other items remained the same. This promise to increase the bread ration had a disastrous sequel, for it coincided with the dock strike in America, and insufficient flour reached the Zone to enable the rations to be honoured. In Wuppertal, for nearly a week, there was virtually no bread in the shops. Hamburg, being a port, was more fortunate, and people living there were able to obtain their rations. In the Ruhr towns the housewives would start queueing outside the bakers' shops at about 6 a.m., but it was more than likely that the shop would never open at all. If it did, perhaps one-third of the waiting women would get served. The situation became better, but now and again, for example during the last weeks in November, in the middle of January, and at the beginning of February, flour supplies once more failed, and the whole town was very short of bread.

The increase in the ration of Nährmittel was regarded by the German people as a poor sort of joke, for no Nährmittel were obtainable. They should theoretically have provided 200 Calories a day.

The German rationing system did not involve registering with a particular retailer, and the people were allowed to buy their food where they liked. The idea behind this was, no doubt, that when food was really short one retailer might have supplies and another not, and those registered with the latter would be unfairly handicapped. As it was, the housewives went from shop to shop in periods of shortage, standing in one queue after another trying to get their rations. Some shopkeepers, of course, kept supplies for special customers, and a great deal of under-the-counter dealing went on, but this could only have benefited a relatively small proportion of the population.

In the 95th rationing period (November 11–December 8) the allowance of potatoes was increased to 10,000 g. and that of Nährmittel reduced to 1,500 g.,

so that the Calories remained at the same level. In actual practice, however, Nährmittel were still not forthcoming, but all persons were officially offered 50 kg. of potatoes to last them for the rest of the winter. These they were usually able to obtain.

With the onset of the extremely cold weather in December, 1946, north-west Germany became frozen and covered with snow. In this cold spell, which lasted until well into April, 1947, there occurred the worst period of food shortage actually observed by the Unit. The official rations for the normal consumer were decreased by about 50 Calories a day during these months. The severe winter made communication very difficult, and not only was it often impossible to obtain the rations, but the population could not travel about and get extra food as they did when the weather was more favourable. With the coming of summer, life became easier again. The rations improved, and more trains began to run, so that it became simpler to travel in the quest for additional food. Milk, however, was still very short, and in fact adults and children over six often got none at all. The winter of 1947–8 was much less severe than the previous one and conditions were on the whole a great deal better. With the currency reform in June, 1948, everything changed overnight, the shops were full of food, potatoes and other vegetables came off the ration, and under-nutrition disappeared.

Means of Obtaining Additional Food

Supplementary rations. The rations for the "normal consumer" in 1946 make rather a poor showing, particularly since they were rarely all available, and the nutritional state of the population might have been very much worse had it not

TABLE 2

Calorie allowances for normal and for some of the special consumer groups in 1946

Consumer group	June–July	July–Aug.	Aug.–Sept.	Sept.–Oct.	Oct.–Nov.	Nov.–Dec.
Adults over 18 years (normal)	1,052	1,137	1,337	1,409	1,550	1,557
Children:						
0–12 months	1,062	1,059	1,059	1,001	1,108	1,138
1–3 years	1,064	1,105	1,189	1,132	1,235	1,211
3–6 years	1,281	1,399	1,377	1,342	1,498	1,507
6–10 years	1,367	1,452	1,652	1,695	1,760	1,771
10–18 years	1,486	1,571	1,771	1,803	1,978	1,944
Expectant and nursing mothers	2,174	2,224	2,424	2,425	2,558	2,567
Moderately heavy workers	1,253	1,338	1,538	1,610	1,750	1,758
Part-time heavy workers	1,415	1,509	1,709	1,867	2,069	2,035
Heavy workers	1,781	1,864	2,090	2,325	2,504	2,513
Very heavy workers ..	2,337	2,445	2,645	2,715	2,874	2,883
Miners:						
Heavy workers ..	2,302	2,386	2,586	2,731	3,203	3,274
Very heavy workers ..	2,892	3,477	3,677	3,822	4,005	3,966

been that few people were living as normal consumers. So many scales of supplementary rations existed that a great many persons managed to qualify for one or other of them. Some of the scales of allowances are shown in Table 2. In the first place there were always supplementary rations for all types of heavy

workers, for persons who worked long hours, and for pregnant and lactating women; wet-nurses were also treated very generously. Children had a special ration scale which included an allowance of 500 c.c. of whole milk per day from 1–6 years of age. Children aged 6–10 were allocated 250 c.c. of whole milk per day, but often did not receive it. Children over 10 were entitled to the adult ration of 125 c.c. of skimmed milk. Most children also received a midday meal at school. This usually consisted of a plate of soup made from beans and soya flour, and was reckoned to provide 300–400 Calories. A special supplement was available to Jews and to anyone who had been in a concentration camp. Civil internees and prisoners also received extra rations from the middle of 1946 onwards, and so did the people who were employed by the occupying forces or by the Control Commission. There were numerous other minor categories, and new ones were added from time to time. Police, prison employees, firemen, ex-members of the Wehrmacht, and all ships' crews were entitled to something extra; drivers of the trams and overhead railway joined the list soon after the Unit reached Wuppertal. There were, furthermore, special rations for all hospital patients and nursing staffs, for patients suffering from certain specified diseases and for attendants exposed to risk of infection, e.g. of tuberculosis. A major amputation entitled a man to extra food, but so did diabetes, a ruling which seems difficult to defend on nutritional grounds alone. Perhaps the most extraordinary supplement, however, was the 30 eggs included in the reward for donating half a litre of blood.

At the time the Unit started to work in Wuppertal, a system had been evolved whereby all patients certified by their doctors as suffering from "hunger oedema", whether at home or in hospital, were entitled to supplementary rations. Table 3

TABLE 3

Supplementary rations for persons suffering from hunger oedema in 1946

	July–Oct.	October onwards	
		First application	Renewal
Milk (g. per week)	3,500	3,500	3,500
Meat „ „	200	300	200
Butter „ „	—	100	62·5
Cheese „ „	—	100	62·5
Bread „ „	500	—	—
Calories per day	485	469	396

shows the composition of these rations, and the number of Calories they contributed to the diet each day. In April, 1946, moreover, the doctors and public were told that a person certified by a doctor as being more than a certain amount underweight for height and age was entitled to receive rations under another scale of "Zulage". Food obtained under both these extra scales of allowances was additional to any other supplementary rations the person might be having.

Other legitimate means. All the supplementary rations so far discussed must have benefited a large proportion of the population, although their value was limited by the fact that they were not always available, but they by no means provided the only legitimate method of getting extra food. No one can

estimate with any degree of accuracy the amount of food that was obtained by unofficial means, but it seems certain that there were very few people in the British Zone in 1946 who did not add to their rations in some way or other. People were encouraged to grow what they could in their gardens. In the large towns, it is true, very few possessed them, but in the suburbs and villages every available inch of ground was cultivated, and the gardens were a scene of great activity during the spring and summer. The German gardens and allotments were on the whole kept extremely tidy and free from weeds. Great precautions had to be taken against thieving and allotment holders took turns to sit up all night and keep watch. Those who lived in or near the country, and who had no garden of their own, were sometimes able to persuade a nearby farmer to plant a row of potatoes for them. At the time when the farmers were lifting their potatoes, people would come from the towns and stand with their sacks at the edge of the field, so that they might start gleaning the moment the farmer gave the word. Those who were fortunate enough to be taken on by the farmer to pick up his potatoes were entitled to some for themselves. At harvest time the cornfields were full of gleaners too, finding something for themselves or their chickens. It was reckoned that one person working hard could glean enough to keep two chickens all the year round.

During the autumn, when the beech-nuts were ripe, a scheme was organized in certain districts whereby the nuts could be exchanged for fat. The children were sent to collect the nuts, which could then be taken to the Food Office, where a definite amount of fat was allowed for each pound. Again, townspeople who practised trades useful to the farmers would go out into the country every now and again and offer, say, to build a barn in exchange for food and lodging. These workmen usually came back weighing considerably more than when they set out. Towards the end of 1946 food parcels began to arrive in Germany from Sweden, America, Canada, Africa, and Switzerland, and later from Britain and Australia. Although these may not have contributed much to the nutrition of the country as a whole, they made a considerable difference to the families who received them, for they provided new flavours and a relief from the monotony of the German rations.

"*Hamstering*". "Hamstering" was probably the most important and interesting way of obtaining food unofficially in Germany in 1946–7. The word has been in use in Germany for many years, and is derived from the name of the common hamster.This rodent, which is indigenous to Europe east of the Rhine, spends most of the summer collecting food which it stores in burrows and eats during the winter. Hamstering was practised extensively during and after the 1914–18 war. It originally implied the laying in of a stock of any kind of goods likely to be short in the future. During the 1939–45 war, and to an even greater degree after it, the commodity which everybody desired to acquire and to store was food. Food of all kinds had been scarce in Germany for years, and the only people who had supplies in any quantity were the farmers. They were supposed to sell all that they had to the authorities, but it was known that a large percentage of the farm produce in Germany in 1946 never reached the markets through legitimate channels. The farmers bartered their stocks with the hamsterers for goods which they needed. Money was of no use to them because they could buy nothing with it, but they, like everyone else, needed clothes, shoes, household goods, machinery, and so on, and they and they alone had something to exchange for these commodities. Townspeople who were able to get hold of

these goods, or who had a stock of them, discovered that a farmer would exchange them for food, and this led to the hamstering system, which went on all over the country on a very large scale during the post-war years.

Anyone associated with the textile industry in Wuppertal, from the workman to the manufacturer himself, could get hold of ribbons and elastic goods, and they became his most valuable asset. The farmers in districts around Wuppertal, however, soon became stocked up with these particular articles, and the Wuppertal people were forced to travel to more distant parts of Germany to get a good rate of exchange. During 1946 the country around Münster and Hannover was considered by the Wuppertalers a good hunting ground, and very profitable exchanges could be made with the farmers there. Gradually, however, even these farmers and their families acquired all the corsets and suspenders they needed, and at the beginning of 1947, after the frontier restrictions had been partially lifted, it was considered better to travel south, to the American Zone. People who had lost all their possessions in the raids were severely handicapped, for not only had they lost any stores of food they might have had, but they had no personal possessions or household goods to offer the farmers in exchange for food. This is, no doubt, one of the reasons why such persons appeared so often at the "hunger oedema" out-patient clinic.

A hamster tour was quite an adventure, and it often involved a great deal of discomfort, especially in winter, for it meant travelling in crowded, unheated trains without windows, sometimes even on the roof of the train or on the buffers. Many changes usually had to be made, and these often involved hours of waiting at stations without any shelter. Sometimes the whole night had to be spent at a station, with no place to sit down. It was generally reckoned that a day and a night were required to reach the hamstering ground. The exchange goods were usually carried in a rucksack. When the hamsterers left the train they usually walked eight or ten miles into the country to get off the beaten track. Those who were fortunate enough to have friends or relations living in the district had a comparatively easy time. The others travelled from farmhouse to farmhouse like pedlars, offering their goods in exchange for any food the farmer had to offer. In 1946 one pair of men's braces was exchanged for ½ lb. bacon, two pairs of suspenders for 1 lb. sausage, and a ball of darning silk for 3 eggs. Three yards of elastic and three yards of fancy ribbon fetched 20 lb. of potatoes, and a pair of corsets 2 lb. of bacon. Just before Christmas a 12 lb. goose was obtained for three pairs of corsets.

After two or three days the return journey was made, and there was always a certain amount of risk attached to it, for hamstering was officially forbidden, and the hamsterers stood the chance of having all their goods confiscated by the police on the train or at the station and being made to pay a fine as well. Children in the towns met the trains with "Handwagen", which they parked in rows outside the stations waiting for the returning hamsterers, and they charged a small fee for transporting the spoils home (Plate VIII).

One or two members of many German families went hamstering every four weeks or so. Generally the second and subsequent trips were easier than the first, for the hamsterer knew at which farms he was likely to get the best rate of exchange for his goods. Some people who did not wish to go hamstering themselves handed their exchange goods over to others who had become experts at the job, and who knew the tricks. These professional hamsterers shared in the food they were able to obtain without having to provide any exchange goods themselves, but there were no money transactions.

The industries of Wuppertal were not all working during the post-war years, and some factories that had survived the raids were working on a very reduced scale. Hence the local commodities were not all being produced freely, and some lines of exchange goods were gradually used up. People then started offering their own possessions, clothes, bed linen, crockery, and cutlery for food. The amount of food that could be obtained for any particular item varied considerably, depending upon the need and greed of the farmer. One farmer would give 3 lb. of fat for a coat, another 4 lb. The energy the German people put into their hamstering activities was amazing. Women frequently came home with 60–80 lb. of potatoes in a rucksack, with bags containing 10–12 lb. in each hand, and they often had to walk miles before they reached the railway (Plate IX). They were usually away from home for four or five days, never sleeping in a bed during this time, and relying upon the farmers to give them their meals. Hamstering, although not officially allowed, was carried on to such an extent that it became an important part of the German national life and all classes participated (Plate X). It was quite independent of the occupying forces, for only German goods were exchanged for food.

The black market. The term "black market", as used in Germany in 1946, implied the purchase or sale of food, either at exorbitant prices or in exchange for coffee, cigarettes or spirits obtained from Allied personnel. The exchange value of these goods varied from time to time. In September 1946 half a pound of butter or a pound of bacon could be acquired for 20 English cigarettes and 10 lb. of flour or 100 lb. of potatoes for half a pound of coffee. Later on when potatoes became scarcer 100 lb. could only be obtained by the surrender of one pound of coffee. This kind of black-market dealing was in the main restricted to the towns, and it was almost impossible to discover the source of the foodstuffs. Only a relatively small number of people could take part in these transactions, since the exchange goods had in the first instance to be bought from the Allied forces for high prices—the value of one cigarette varied from 5–10 RM. Others, who had no access to cigarettes, coffee, or spirits, paid directly in money for extra food. One man, for example, earning 35 RM a week, spent 16 of them on 1 lb. of brown flour. This was considered cheap, for 25 RM per lb. was the more usual black-market price. White flour cost 20–30 RM per lb., butter 180 RM per lb., and coffee 300–500 RM. Tea cost 1 RM per g. Some people in the professional classes counted on spending almost the whole of their earnings on food in the black market, and there is no doubt that most of those who could afford it obtained some extra food in this way.

Arrangement of Meals

In most German households breakfast consisted of one or two slices of bread, spread with a little jam, and one or two cups of "Ersatz" coffee without milk. For the midday meal the people ate boiled potatoes and vegetables, often cooked together as "Eintopf", or else they had soup. Many workers ate their "Mittag" in their works' canteens, giving up the appropriate number of coupons, but vegetables or soup always formed the basis of the meal. At about 4 o'clock those who were at home usually ate a slice or two of bread, with a smear of jam, and they had a cup of "Ersatz" coffee as well. The evening meal was eaten at about 7 p.m., and it often consisted of the remainder of the midday "Eintopf" or soup and a slice of bread. The favourite dish was fried potatoes, and the German people preferred to use their fat ration, even their butter, for frying potatoes than for spreading on bread. Sweet soups were very popular and were

made whenever the rations allowed, but the shortage of Nährmittel and of milk made it impossible for the German housewives to make them as often as they would have liked. The fish and cheese rations were generally eaten with bread for the evening meal. Part of the meat ration was sometimes bought as "Wurst" and eaten with bread for supper, particularly on Saturday nights, but most of it was always reserved for the Sunday midday dinner. It was first fried, generally all in one piece, and then stewed, and it was always served with plenty of thick brown gravy. Potatoes and vegetables were also eaten for the Sunday midday meal—most people preferred to have a good meal then and to go short on other days. In some households a pudding was also served. This might be made from semolina, skimmed milk and a little sugar, or it might consist of stewed or bottled fruit. All German housewives who were able to obtain fruit during the summer or autumn bottled as much as they could. "Kaffee" on Sunday afternoon included some kind of very plain home-made cake whenever possible, but the evening meal was similar to that on other days.

Special occasions always called for special efforts, and it was a puzzle sometimes to find out the source of all the food. On Boxing Day, 1946, for example, one of the German laboratory technicians gave a Christmas party, and one of the members of the Unit was invited. The meal included a large apple tart with pastry above and below, a sponge sandwich with jam inside and chocolate cream on top, an iced currant loaf made from white flour, and small pastries of assorted shapes and sizes. This was accompanied by "Ersatz" coffee with cream and sugar. Another member of the team was invited to a wedding party in February, 1947, in a working-class home in the neighbourhood of Wuppertal. About 25 people were present, and one luscious iced cake after another was brought forward, so that all the guests could have eight or ten large slices if they so desired—and most of them did.

These are two examples of plenty in the midst of hunger, but they were by no means exceptional. Birthdays, betrothals, and anniversaries of weddings, all involved some form of "Fest". Special hamster tours were often undertaken beforehand to obtain food for the occasion, and there is no doubt that black-market activities were frequently pursued.

During the years 1946–7 the German family was a very definite self-contained food unit. Any extra rations to which one member might be entitled were usually shared by them all. Thus, the whole family generally participated in the pregnant women's "Zulage", in the father's rations as a heavy worker, and even in the younger children's milk. They did not share their extras with other families, however, and if a family was given a present of foodstuffs, all members took great pains to prevent other people knowing about it. Many German families were visited during the time the Unit was working in Wuppertal and some small present of food was often taken. This was usually put away out of sight at once, but if it happened to be lying on the table and a knock came at the door it would be whisked away immediately and hidden. This was observed again and again, in all types of homes. It may have been a carry-over from years of Nazi rule, when no man could trust another outside his own family circle. It is well known, however, that among a starving population each man is interested only in acquiring food for himself, and he will steal food even from his best friend (*McCance*, p. 21). In Germany there was no real starvation, and the people never reached this second stage of famine, but food was short and extras were very precious. The individual could still consider others beside himself, but his interests were confined entirely to his own family circle,

and each member of the family was anxious not to have to share his luxuries with outsiders.

LABORATORY FACILITIES

One of the main reasons for deciding to establish the Unit in Wuppertal was the fact that working space was available in the laboratories of the I.G. Farbenindustrie in Elberfeld (Plate XI). An unoccupied set of rooms was placed at the Unit's disposal; they consisted of well-equipped laboratories with steam, compressed air, and vacuum laid on to all the benches, a dark room with photometric apparatus, a good refrigerator, a large office with tables, desk, typewriter, and telephone, and also a smaller office. Dr. G. Hecht was detailed to look after the Units'requirements, and he did this so well that the whole of the services of the I.G. seemed to be at the Unit's command. The library facilities were one of the great assets of the place. All the usual medical and physiological journals for the pre-war years were obtainable except some of those dealing with children, and some of the latter were taken by one or other of the two municipal hospitals. German technicians were engaged to help with the laboratory work, and several remained with the Unit for the two and a half years they were in Wuppertal. Mrs. M. Sitnik, a German interpreter-secretary, also worked with the members of the Unit the whole of this time; she returned with them to Cambridge and gave much assistance in the preparation of this report.

SOURCES OF SUBJECTS AND MATERIAL

Hospitals

Städtische Krankenanstalten, Barmen. Through the courtesy and co-operation of Professor Sturm, three small wards adjoining each other and holding in all 16 beds were set aside for the Unit in the municipal hospital at Barmen. The German sister and nursing staff, who were extremely co-operative throughout, undertook the routine care of the patients, but the Unit's own nursing sister, Miss L. A. Thrussell, was responsible for all the special work. The staff of the hospital made any determinations of basal metabolic rate, electrocardiograms, Wassermann and similar tests asked for by members of the Unit, but all the clinical and chemical work and all the special investigations were done by members of the Unit. All syringes, needles and similar instruments were provided by the Unit and sterilized in the I.G. laboratories. The X-ray department of the hospital was set aside for the Unit's use one day each week for a period of three months; all films and chemicals for developing were brought out from England.

The members of the Unit obtained a great deal of help from Dr. Dorothy Rosenbaum, who acted as their resident medical officer at Barmen. She was loyal to a degree, completely bilingual, and her efficiency and advice were invaluable on many occasions.

It was arranged with the Medical Officer of Health of the town that all persons certified by their doctors as suffering from hunger oedema, and applying for supplementary rations on this account, should attend an out-patient clinic held by the Unit two mornings a week at the hospital before their extra rations were granted. The space available for seeing these people was rather limited, but all who came were interviewed by two members of the Unit, often assisted by Dr. Rosenbaum. The urines of all patients were tested for albumen by a German technician attached to the Unit. Some of the applicants were fully

examined when first seen, and some were admitted to the wards for further investigation. On the whole this system was satisfactory in that it provided plenty of cases of undernutrition for investigation, but it over-emphasized the importance of oedema, and thus led to considerable selection of material. Later on, therefore, arrangements were made to see people who were applying for extra rations on grounds of loss of weight.

Landesfrauenklinik, Wuppertal. Arrangements were made to work at this hospital to study the effects, if any, of undernutrition upon the weights of babies at birth and upon the production of milk during the puerperium. Professor Anselmino, the Director, placed every facility at the disposal of members of the Unit. Dr. von Finck, one of his assistants, spent part of her time helping with this and other investigations, and was paid a small honorarium for her services. Various aspects of the physiology of infancy were studied at the Landesfrauenklinik while the Unit was in Wuppertal, and for this purpose isolated cases were also provided by the Städtisches Krankenhaus, Elberfeld, and the children's hospitals at Duisburg and Krefeld.

Ronsdorf Lazarett. This was built as a barracks during the war. When the Unit first arrived in Wuppertal it was being used as a general hospital, but later part of it was devoted to prisoners of war returning from Russia, and many of the studies on these men were made there. There again the medical and nursing staff were most co-operative, and put all their facilities at the disposal of the Unit.

Allgemeines Krankenhaus, Langenhorn, Hamburg. During our first visit to Germany in the spring of 1946 we made a few preliminary investigations on undernourished patients in this hospital through the courtesy and co-operation of Professor Bansi. These investigations included kidney and liver function tests, and the collection of samples of blood for cholinesterase determination and for electrophoretic analysis.

Infant Welfare Centres and Children's Homes

To obtain information about the length of lactation and to study the composition of human milk, it was necessary to work through the infant welfare centres. Contact was established through the Landesfrauenklinik and the local paediatricians, and the welfare workers arranged that the mothers in whom the members of the Unit were interested should be visited in their homes. The welfare workers also kept record cards showing the length of time the mothers were able to feed their babies.

Augustinusstift, Wuppertal. This was a Roman Catholic home for young children, but it also accommodated a few unmarried mothers for a short time after the birth of their babies. Some of these women were given dietary supplements to study their effect on the composition of breast milk. Dr. Gierlich and the nuns in charge helped in every possible way.

Städtisches Waisenhaus, Duisburg. This was the municipal orphanage, and it accommodated about 180 children. Most of these children took part in a dietary experiment to be described in a later report, but a few, who were admitted too late to be included in this investigation, and who were living on the ordinary German rations, were used in a study of the absorption and excretion of calcium and other minerals.

Städtisches Kinderheim, Landhaus Linde. The large orphanage in Wuppertal was completely destroyed during the raids, and the children were living in three smaller homes. One of these, Landhaus Linde, housed about 60 children aged

4–14 years. The effect of adding calcium to the bread of half these children for a period of six months was investigated.

Civil Prisons

During the first half of 1946 the long-term inmates of the civil prisons were seriously undernourished. They had been provided with the same rations as the German normal consumer, but, unlike him, they had been unable to supplement their official rations in any of the hundred and one ways that seemed to be available to a free man, and they had in consequence, gone downhill very much faster. In April 1946 we paid a visit to the prison at Kiel and took samples of blood from 15 of the prisoners. Later on, permission was obtained to visit the big civil prison at Siegburg and to make some investigations there. Unfortunately Siegburg is 45 miles from Wuppertal, but the cases were so suitable and the staff so co-operative that a considerable amount of work was done there, particularly on the production of immune bodies, on renal function and on skins. Each prisoner was asked for and gave his consent before any investigation other than a superficial clinical examination was made upon him.

Civil Internment Camps

Three civil internment camps were visited in the spring of 1946. Some of the inmates in each camp were examined clinically, and samples of blood were taken from 12 men in the camp at Sandbostel and from 12 at Westertimke, both in north Germany.

Factories and Industrial Undertakings

Through the co-operation of Dr. Lange, who was in charge of factory personnel, 81 employees of the I.G. Farbenindustrie, Elberfeld, were interviewed, examined and tested in various ways. The factory workers and staff in this group were better off nutritionally than many of the other local people, since they received help from the firm. They were able to obtain a midday meal, for instance, in the works' canteen, and this was a good exchange for the ration coupons the men were asked to surrender. The firm also supplied its staff with some goods on favourable terms, and found them somewhere to live. A comparatively large proportion of the employees, many of whom were related to each other, had been with the firm for many years.

Normal Controls

The local Army units and the 77th British General Hospital were approached from time to time and provided a certain number of normal controls. The members of the Unit were used for this purpose as much as possible. Some of the material required was obtained in England, and German prisoners of war in England and English hospital patients gave their services for several investigations.

THE CLINICAL PICTURE

Adult Civilians

The object of the Unit was to study the effects of undernutrition on individuals or small groups. No attempt was ever made to survey the entire population or to determine the incidence of undernutrition or of hunger oedema in Wuppertal. It is, however, known that the people seen at the out-patient clinics were representative of those applying for supplementary rations on account of oedema,

for nearly all who applied on these grounds for the first time were seen. The persons who came to the out-patient sessions were all asked to give their age and their pre-war or "normal" weight, and their present weight and height were accurately measured. The aspects of undernutrition which were of interest tended to change from month to month, and the time available for each applicant naturally varied with the numbers presenting themselves on any particular day, but inquiries were generally made into each person's circumstances, his work, the numbers in his family and the rooms at its disposal. Questions were asked about nocturia, giddiness, hunger, sweating, and anything else that seemed important at the time. The patient's skin was examined and his reflexes observed, and sometimes his heart and blood pressure were tested. Where anaemia was suspected a check was made by determining the haemoglobin, and by a cell count. Applicants were occasionally examined more fully if there seemed any good reason for doing so. Cases were then selected for the various physical and psychological investigations.

It was noticed before very long that most of the people applying for supplementary rations belonged to the older age groups of the general population, and of these there were more men than women. Careful inquiry generally brought out some good cause for the failure of these people to obtain enough food. They were too frail or old, perhaps, to stand in the queues, or they lived alone and depended upon some "Gasthof" for their meals; they were too poor to buy on the black market or too conscientious about their work to take time off for any of its activities; they had a spendthrift or an invalid wife, no garden, or they were maimed in some way or other. Reasons like these usually lay behind the application for supplementary rations. Few children came to the clinic, and none of those seen was considered to have hunger oedema.

The out-patient clinics were continued for almost two years. During this time 1,407 civilian persons applying for extra rations for the first time were seen. Many came for renewals, and the total number of visits over the two years was 1,941. Of the 1,407 new applicants, 805 were men and 602 women. Table 4

TABLE 4

Numbers of men and women in different age-groups attending the out-patient clinic

(New patients—excluding repatriated prisoners)

Date	Numbers attending out-patient clinic					
	Men			Women		
	Under 40	40–60	Over 60	Under 40	40–60	Over 60
19.8.46– 2.2.47	41	154	200	46	127	81
3.2.47–20.7.47	32	99	108	49	100	60
21.7.47– 4.1.48	19	46	40	18	39	23
5.1.48–30.5.48	18	27	21	16	27	16
Total ..	110	326	369	129	293	180

shows their age distribution, and the numbers who were seen during the four 24-week periods when the out-patient clinics were held. Eighty-six per cent of the men and 79 per cent of the women were over 40 years old. The numbers fell off steadily as time went on, and more than three-quarters of the men and women were seen for the first time during the first twelve months.

The signs and symptoms observed in these people had all been seen and described many times in the past (*McCance*, p. 21). Pallor was a characteristic sign, particularly among the men and older women (*McCance and Barrett*, p. 83), and it was usually obvious that there had been a considerable loss of weight. On the negative side, there were no signs of vitamin deficiencies and there were no complaints of diarrhoea. Most of the women under 40 said that they were menstruating normally, although several who had previously been prisoners in Russia stated that they ceased to menstruate during their captivity (Dean, 1949). There were, in fact, none of the signs of really severe undernutrition, and no deaths which could be attributed simply and solely to this cause occurred either in Wuppertal or in the whole of the British Zone.

Some of the more important positive findings will now be dealt with under separate headings.

Oedema. The oedema was usually confined to the legs, and ascites was only demonstrated in one man. The legs were often more or less free of oedema in the morning, but filled up towards evening or after much standing. It is of interest that no patients noticed that their legs got worse in hot weather. The oedema of the legs was very mobile, as was shown not only by the ease with which pits were made with the examining fingers, but also by the strict relation which it bore to the tightness of shoes, boots and garters. Any constricting band on the legs or feet was likely to be overlapped by a rim of swelling. As the clinics were held in the mornings it was always possible for the patients to claim that the oedema was not being seen at its worst, and the natural tendency to exaggeration sometimes produced rather amusing results. It was obviously to the advantage of both the patient and his doctor to magnify the oedema, and some patients would indicate, in their efforts to convince the examiners of the size their legs reached at night, circumferences which were far in excess of anything actually seen in any patient admitted to hospital. One man was so carried away that he indicated the natural curvature of his calf muscles as an instance of "Wasser".

For clinical purposes the oedema was graded into five categories: (1) Detectable pitting over the ankle or shin; (2) pitting obvious but slight, and confined to the lower parts of the leg; (3) pitting to the knee; (4) considerable swelling, up to the knee or above; (5) gross oedema of the whole leg.

A few patients had oedema of the eyelids and said this had been worse when they got up. Some women, especially during the winter months, said their faces became swollen during the night, and that they were bigger on the dependent side. Some evidence of the truth of this was obtained by making measurements of various parts of the face in the evening and again in the morning while the patient was still in bed.

The impression was gained that there was possibly some correlation between body build and the presence or absence of oedema, and that the stout, heavy type of person was more likely to get oedema than the slim one. It is difficult to be certain about this, but the people applying for supplementary rations because they were more than 20 per cent underweight were generally those who had always been thin, and they rarely showed signs of clinical oedema. On the other hand, the persons who applied for extra rations on account of their oedema had often been grossly overweight in times of plenty, and their average pre-war weight had undoubtedly been greater than that of the other group. This is illustrated in Table 5, which is described in the next section.

Loss of weight. It was generally quite obvious that the patients had lost weight. Their collars often seemed ridiculously large, and their waistcoats, coats and trousers frequently looked as though they had been made for another and much larger person. Sometimes the ribs were so prominent that it was difficult to find a flat area of the chest over the apex-beat on which to rest the stethoscope. In order to discover whether the weight loss bore any relation to the person's previous weight, the weight losses of 68 men and 13 women, who were applying for extra rations because they were underweight, were compared with those of a similar number of men and women of the same ages who were applying for supplementary rations for hunger oedema. Table 5 summarizes the findings.

TABLE 5

Relation between pre-war body weight, loss of weight, and oedema

	Persons applying for extra rations because they were underweight		Persons applying for extra rations because they had oedema	
	Men	Women	Men	Women
Average age (yr.) ..	53	51	53	51
Average height (cm.)	171	159	171	160
Previous weight (kg.)	73·1	61·7	79·6	75·8
Present weight (kg.) ..	59·3	47·6	66·2	58·1
Loss of weight (kg.) ..	13·8	14·1	13·4	17·7
Loss as percentage of previous weight ..	18·9	22·8	16·9	22·3

The average heights of the men and women in the two groups were similar, but the underweight applicants had weighed considerably less than the others before the war. This is particularly striking in the case of the women. The men in the two groups had lost similar amounts of weight, but the heavier women had lost considerably more than the light ones.

Pulse rate. One of the most definite findings in the patients seen in the out-patient clinics was the slowness of their pulse rates. The circumstances of the examination, moreover, were not so restful that the pulse was reduced to its lowest possible level. Nevertheless, pulse rates of 60, 50 and even fewer beats per minute were not uncommon in the ordinary Wuppertal civilian. The pulse rates of the patients admitted to hospital, taken in bed, were also low, and had a mean value of 58 beats per minute (S.D. 7·0) for 66 men whose ages ranged from 24 to 76 and averaged 52 years.

Basal metabolic rate. It was a common statement among the German physicians that hyperthyroidism almost disappeared during the time that food was short (Heilmeyer, 1946). Determinations of basal metabolic rate were made as a routine on many of the patients admitted to the wards. The Knipping apparatus belonging to the hospital was used to measure the consumption of oxygen and the output of carbon dioxide. The basal metabolic rates of 70 under-nourished men, in whom no complicating illness could be discovered, were estimated when they were first admitted to hospital for various investigations in July and August 1946. Their oxygen consumption per square metre per minute averaged 108 c.c., and their carbon dioxide output 85 c.c. When these results were compared with the Sage (Aub-Du Bois) standards (Du Bois, 1936), the average basal metabolism was found to be 82 per cent of normal.

Blood pressure and other vascular findings. There was a tendency for the undernourished patients to have systolic and diastolic pressures that were on the low side of normal. The blood pressures of the people admitted to hospital were measured under conditions of rest, and the average pressure of 54 men aged 24 to 76 years, with an average of 51 years, was 113/70 mm. Hg (S.D. systolic 16, and diastolic 9).

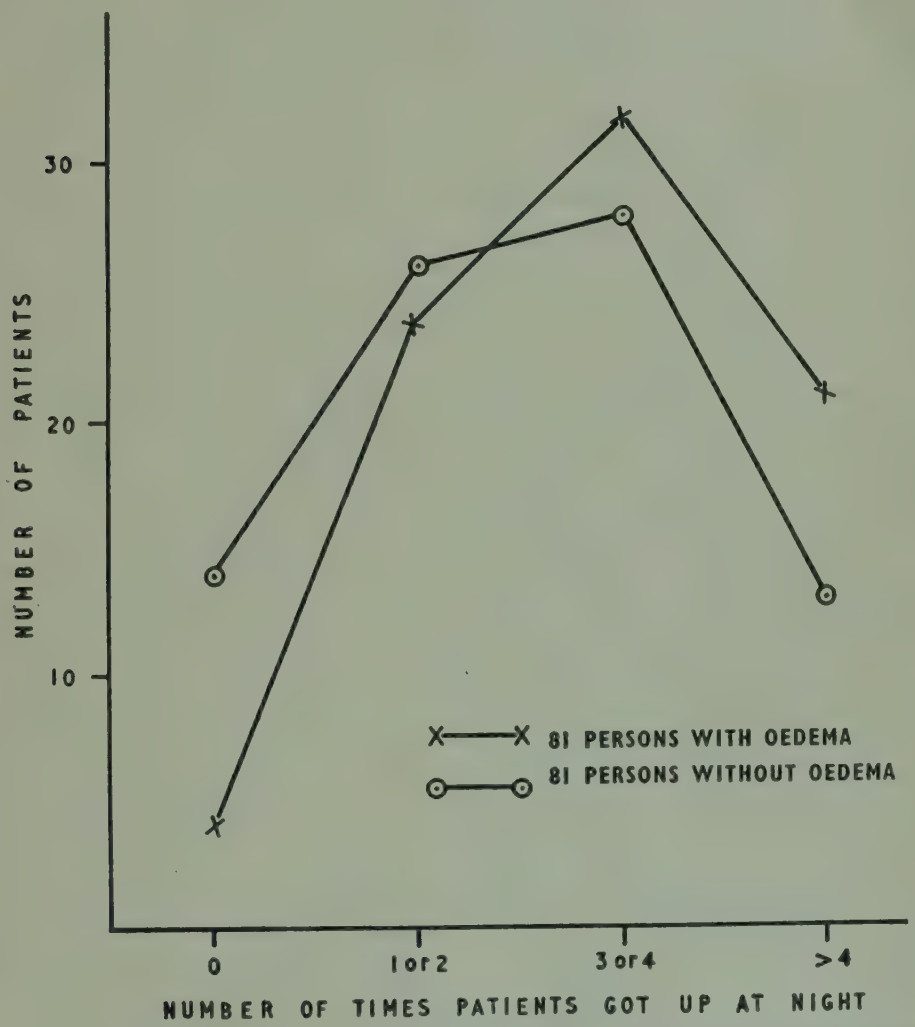

FIG. 1. Frequency distribution diagram of nocturia in persons with and without oedema.

Nocturia and polyuria. Almost every patient complained that he had to get up several times during the night to empty his bladder, and there was no doubt of the truth of this, for all the patients admitted to hospital for investigation had to pass water during the night. This nocturia affected people who had oedema and those who had none, but Fig. 1 shows that a person with oedema tended to have to get up more times each night. The 81 persons in the two groups were paired as regards age and sex and their weight losses have already been discussed.

Tendon reflexes. One of the most striking observations made on the patients who were attending the out-patient clinic or had been admitted to the wards was the briskness of the tendon reflexes. This was made the subject of a special study, and the findings are described by *McCance and Dean* (p. 140) and *Davis* (p. 147).

Skin changes. The most common lesion was desquamation, together with some hyperkeratosis pilaris. The changes are described in detail by *McCance and Barrett* (p. 83).

Haemoglobin levels. Haemoglobin determinations by the alkaline haematin method (Gibson and Harrison, 1945) were made on a large number of the patients admitted to hospital for various investigations. The average value for 55 men was 12·6 g. per 100 c.c. (S.D. 1·7). This figure is on the low side of normal. The blood was collected when the patients had been lying in bed for varying lengths of time (Widdowson and McCance, 1950).

Repatriated Prisoners of War

The first prisoners of war from Russia returned to Wuppertal in August 1946, and from then until the Unit left Germany in January 1949 they were coming back almost continuously. In 1946 and 1947 very few men returned unless they were unable to work, but as time went on the returning prisoners were more and more physically fit. This was partly because the worst were sent back first, but also because most of those who came back in 1948 had spent many months in hospitals and rest centres in Russia before they were repatriated.

The ex-prisoners of war were automatically given extra rations for three months after their repatriation, but many were also sent by their doctors to the out-patient clinic for further supplementary rations on account of their oedema. Nine hundred of these men were seen, 165 in the first six months, 134 in the second, 222 in the third, and 379 in the fourth. By the beginning of 1948 far more ex-prisoners than civilians were attending the out-patient clinic and, in fact, they represented 75 per cent of all new patients.

Like the civilian patients, the repatriated prisoners were nearly all working-class men, and very few officers were seen. Seventy-five per cent of them were under 40, and none was over 60, so that they represented a younger age group than the civilian men. It was usually possible in 1946 and 1947 to distinguish at sight in a crowd of out-patients those men who had recently returned from Russia, not merely because of their age or dress, but because they had a very characteristic look of dullness and apathy. When spoken to they answered slowly, although their understanding appeared to be perfect, and their movements tended to be somewhat deliberate. Other patients often gave an appearance of greater misery, but were usually more responsive and alert. Many of the ex-prisoners seemed to have no interest in anything and no desire to make a new start. Some of them had oedema, which did not disappear even after they had been back some time and had grown very fat. When these men returned to Germany they generally weighed less than they had done when they were in the German army, but most of them said that they had already put on a considerable amount of weight by the time they appeared at the out-patient clinic. The rapid gain of weight in these ex-prisoners of war was one of the most noticeable features about them, and it is discussed more fully by *Hutchinson, McCance and Widdowson* (p. 216), *McCance, Dean and Barrett* (p. 135), *Widdowson and McCance* (p. 165), and *Widdowson and Thrussell* (p. 296). It was probably the result of eating a great deal of food coupled with complete inactivity. They had enormous appetites and their friends and relations went to considerable lengths in their endeavours to satisfy them. It was never established that their basal metabolic rates were particularly low and, in contrast to the civilian patients, their pulse rates, taken in the out-patient clinic, were rather rapid. The average

pulse rate of 32 ex-prisoners, aged 21 to 51 years, taken in bed, was 70 beats per minute. Their blood pressures averaged 118/73 mm. Hg.

The ex-prisoners, like the civilian patients, complained of nocturia, but they generally agreed that this had been even worse while they were in Russia. More of them than of the civilians had abnormal skins, and besides hyperkeratosis and desquamation they often had furunculosis and evidence of chronic ulceration, most of which had healed before they returned to Germany. These abnormalities are described by *McCance and Barrett* (p. 83)

Very many of the men complained that they were short of breath on exercise, even if the effort were very slight, and it was common to see them overbreathing when they sat down for examination after the walk of a few yards from the adjacent waiting-room. Even more striking, however, was the way they started to sweat on the slightest mental or physical exertion. The sweat poured off them as they were being questioned. Most of them said that this tendency to sweat had begun when they got home, or perhaps on the return journey. Very few had noticed it in Russia, and it seems certain that it was psychological in origin. It is dealt with in detail by *Davis* (p. 147).

Civilian Prisoners

As has already been explained, prisoners fared less well than the German normal consumer because they had no means of supplementing their rations. Twelve prisoners, aged 24 to 66 years, in a civilian prison at Kiel, were examined in April 1946. Six of them had oedema and six had none, but they were all emaciated and in a worse state of nutrition than any other group of persons seen in Germany. Their average height was 170 cm. Their average weight in health had been 70 kg., while on examination it was only 47 kg. in spite of the oedema. They showed all the skin changes described by *McCance and Barrett* (p. 83).

In June 1946, and again two months later, 25 men aged 17 to 58 years were examined in Siegburg prison. These men had all been in prison for at least three months. Seventeen of them showed signs of clinical oedema in June and 18 in August. Their weight in times of plenty and before their imprisonment averaged 74 kg., in June 1946 it averaged 53·7 and in August 54·8 kg. The blood pressures and pulse rates were measured after the men had been sitting quietly in a chair for at least an hour, and had then lain down for five minutes. The blood pressures averaged 118/73 mm. Hg in June and 100/66 mm. Hg in August. The mean pulse rate was 53 beats per minute.

The skin changes seen in these men are described by *McCance and Barrett* (p. 83) and other investigations that were made on them by *Gell* (p. 193) and *McCance* (p. 175).

Children

During 1947 some hundreds of children living in various orphanages were examined clinically as a preliminary to feeding experiments, and it is probable that these children were typical, to a greater or lesser degree, of all children living on the German rations. They were nearly all short and light for their ages, when compared with English and American standards. The older children were worse than the younger ones, and the boys worse than the girls. In other respects the children seemed normal and healthy. They were as lively as any other children and did not appear to suffer unduly from minor illnesses. Some of them showed hyperkeratosis, particularly of the upper arms, and they tended to have a fair amount of skin sepsis, but this may have been caused more by lack of soap and dressings than shortage of food.

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II. THE HISTORY, SIGNIFICANCE, AND AETIOLOGY OF HUNGER OEDEMA

by R. A. McCance

INTRODUCTION

One of the reasons for man's ability to colonize practically the whole of the world's land surfaces has been his adaptability in matters of food. His omnivorous nature and his intelligence and forethought have enabled him to withstand seasonal shortages of his usual foods that might otherwise have been exterminating, and even to survive serious failures of his crops. Nothing, however, has protected him completely or for long from the fear or the reality of famine. History is full of references to famines, and literature from the earliest times contains the most graphic accounts of them. But famine has never been described alone; pestilence has been coupled with it in men's minds at least since the times of Herodotus (*c.* 450 B.C.) and of Hesiod (*c.* 700 B.C. a).

τοῖσιν δ'οὐρανόθεν μέγ' ἐπήγαγε πῆμα Κρονίων
λιμὸν ὁμοῦ καὶ λοιμόν: ἀποφθινύθουσι δὲ λαοί.

The use of words with cadences and meanings so similar as those of λιμός and λοιμός naturally made for ambiguity in the interpretation of prophetic utterances (Thucydides, *c.* 400 B.C.), and the horrors of war, pestilence and famine have always been associated in literature and art.

Apart from any direct effect of undernutrition on man's ability to withstand disease (Kisskalt, 1914; *Gell*, p. 193), it is easy now to see the reason for this association. War has always led to the movement of troops and civilians, and hence to disorganization, destruction, and overcrowding. Susceptible populations were invaded by disease and the crops were not sown or harvested. Even apart from war or political strife (Fisher, 1927), failure of the crops from drought, floods, or blight inevitably meant movements of the population, overcrowding, and misery—just the conditions, in fact, to favour the spread of the great epidemic diseases, such as plague, cholera, dysentery, smallpox, and typhus (Erismann, 1879; Lammert, 1890; Kisskalt, 1914, 1915; Gottstein, 1922; Mühlens, 1923a, b; Mallory, 1928; Asquith, 1943).

During the first 6 months of that dark period one third of the daily population of our streets [Cork] consisted of shadows and spectres, the impersonifications of disease and of famine crowding in from the rural districts, and stalking along to the general doom—the grave—which appeared to await them but at the distance of a few steps, or a few short hours. (Callanan, 1849.)

The laws of economics ensure that a shortage of food means a rise in its price, and this has always been emphasized in the literature as one of the accompaniments of famine. "A measure of wheat for a penny, and three measures of barley for a penny" (Revelation, VI, 6). The value of a bean to two Crusaders at the siege of Acre in 1190 has been immortalized in the story of the men who bought 13 for a denarius. On getting to their camp they found that one bean had a weevil in it, so they went back to the trader and forced him to replace it (De Vinsauf, *c.* 1192 A and B). Wilken (1826), the pioneer historian of this period, attributed far too great a value to the beans by stating that the denarius was a gold coin, but no bean, however valuable, could have made good the Calories that must have been expended by the two Crusaders in replacing the one with the weevil in it! Examples such as these could be multiplied indefinitely,

but they have little meaning without a knowledge of values and purchasing power. Price fluctuations are more informative and were often extremely large when communities depended upon local supplies. The records kept by Reiner of Lüttich, for instance, show that the price of a modius of rye fell from a famine peak of 40 solidi in July, 1197, to one of 3·5 solidi in a season of plenty three years later. There is a slight uncertainty about this comparison, because some revaluation of the currency took place in the autumn of 1198, but the grain prices do not appear to have been affected to any extent. Rye was selling for 1·25 solidi per modius in 1209 (Curschmann, 1900).

The shortage of food may be absolute, as it is during a siege, or relative, as it was during the great Russian famine of 1891, for instance, when although rye bread could be bought freely in Novo Terenka for three farthings a pound, even this price was completely out of reach of the landless peasants who had no money at all and were consequently dying of starvation (Stevini, 1892). In the Irish famine also (Nicholson, 1850; O'Rourke, 1875), food could be bought in the country and the hotels were open, although the poor people were dying in thousands in the streets and cottages.

A further matter which figures prominently in all the accounts of observers is the nature of the food to which men may be driven by hunger. Dogs, cats, rats, hay, offal of all kinds and even the bodies of children and adults have been eaten again and again (Fisher, 1927). "Give thy son, that we may eat him today, and we will eat my son tomorrow" (II Kings, vi, 28).

> This year it was cruel; . . . the people ate lime tree leaves, birch bark, pounded wood pulp mixed with husks and straw; some ate buttercups, moss, horse flesh; and thus many dropping down from hunger, their corpses were in the streets, in the market place, and on the roads, and everywhere. . . . Woe and misery on all. Fathers and mothers would put their children into boats in gift to merchants, or else put them to death; and others dispersed over foreign lands. (*Chronicle of Novgorod*, 1016–1471.)

Lammert (1890) gives a gruesome account of the depths to which men sank during the Thirty Years War, but deeds such as were done then have not been confined to Europe or the Middle Ages. Sometimes the "foods" are priced: "an ass's head was sold for fourscore pieces of silver" (II Kings, vi, 25); a quarter of a dog, fattened by eating the bodies of the Irish slain, was sold for 5s. 6d. at the siege of Derry (Walker, 1689); a common rat fetched two francs, and a long-tailed one 2·5 francs in Paris in November, 1870 (Washburne, 1887). The figures tell us little without comparative prices, but they show the lengths to which men were driven when famine stalked abroad.

The *Encyclopaedia Britannica* (1929) defines famine as "an extreme and general scarcity of food, causing distress and deaths from starvation among the population of a district or country". This is a fair enough definition, but it conveys nothing of the misery of some of the lines in the *Chronicle of Novgorod* (pp. 11, 54, 74–6), nor does it take account of the smaller loci where undernutrition and famine may have flourished. In these, often man-made, microclimates many people have starved for one reason or another, often in the midst of plenty. Prisons, ships, asylums, concentration camps, exploring parties, diseases such as anorexia nervosa—all these have a rich literature and provide information and evidence about diets and undernutrition.

It is now well known that oedema frequently accompanies undernutrition. The two, in fact, have become closely associated in men's minds, and a great deal of work has been done on the causes and effects. Before enlarging upon this, it is necessary to define the terms more clearly, and it will be valuable to discuss why the association, which must always have existed, should have received so

little notice until recent times. That this is so is shown by the fact that oedema is mentioned neither by Prinzing (1916, 1931) nor Dumas and Vedel-Petersen (1923), whose books are concerned with the diseases, famines, and deaths caused by wars. It finds no place in the *Medical and Surgical History of the British Army which Served in Turkey and the Crimea* (Army Medical Department, 1858), except in connexion with scurvy. Nicholson (1850), Washburne (1887), and Stevini (1892), who were all eye-witnesses of great famines and must have discussed the effects, do not record it. Even Kisskalt (1914) says nothing about it in his excellent article on "Hungersnöte und Seuchen". The same is true of most of the articles on diets and diseases in prisons and ships (Howard, 1784; Good, 1795; Penitentiary at Milbank, 1823; Inspectors of Prisons, 1836; Budd, 1841–2; Böhm, 1869). Yet the diets in prisons were generally very bad owing to the feeling that the diet should be part of the punishment and to the desire to keep expenses low, and also because of the general corruption which seems to have been inseparable from prison administration until well on in the nineteenth century (Howard, 1784; Good, 1795; Combe, 1837; Baly, 1845; Beneke, 1853; Falger, 1867; Baer, 1876, 1899; Voit, 1876; Cless, 1879; Kisskalt, 1912). Even to the scientists interested in undernutrition (Chossat, 1843; Mühlmann, 1899) oedema was a matter of small concern.

One of the reasons why oedema received so little attention in the past goes far towards explaining its prominence in recent times. While the ravages of plague typhus, smallpox and dysentery were so dramatic and overpowering, and while the prisons were such hotbeds of vice, corruption, and disease, it was natural enough that oedema should take a second place and be mentioned only rarely or confused with one or other of the signs of an acute infection. The improvements in preventive medicine which have marked the last 80 years have largely abolished the great famine diseases and thus unmasked the metabolic accompaniments of undernutrition which had remained unrecognized before. There are other reasons for the prominence now assigned to oedema, but these will be discussed later.

Nutritional Oedema other than Hunger Oedema

Although the term "nutritional oedema" is often used as if it were synonymous with "war", "hunger", "famine" or "inanition" oedema, its use in this sense is unfortunate, for there are several different disorders of nutrition which give rise to oedema, and the oedemas have been confused. "Whenever there are wars, famines, and long voyages in ill-equipped ships; wherever persons are housed together under relatively bad conditions, as in asylums and prisons; wherever the population lives on a minimal or one-sided dietary liable at times to be reduced to a fraction above nothing, there we have the conditions for the development of food-deficiency diseases, and there we have epidemic dropsy" (Bigland, 1920). If the word "epidemic" is omitted, and if it is appreciated that the dropsy may have been due to three or four different causes, this becomes a splendid generalization, but as it stands it is only misleading, for it is essential to separate clearly the various types of nutritional oedema before beginning to discuss any one of them (Nixon, 1920b). It is now accepted that persons suffering from a deficiency of Calories or proteins may become oedematous. They need show no signs of any vitamin deficiency. This is the condition which will be referred to as "hunger" or "inanition" oedema. The terms "war" oedema and "famine" oedema are unsatisfactory, since the syndrome has no direct connexion with war and has frequently been recorded apart from the state of affairs

suggested by the word "famine". "Hunger" is therefore a better epithet than "famine" and has the merit of brevity and use. "Inanition", while having the same meaning as "hunger", is rather longer and sounds a little pedantic in English.

Beriberi. Oedema is well known to be a part of the beriberi syndrome, in which it is generally considered to be due to a deficiency of aneurin. There need be no Calorie deficiency. It is this form of nutritional oedema which was such a problem in the Japanese navy, and in prisons in India and other tropical countries (Hunter, 1807; Cornish, 1865; Committee of the Lister Institute and the Medical Research Council, 1932). The association with rice diets goes back a very long way, as the papers of Hunter and Cornish show. There were a great many cases during the second world war among Europeans who were prisoners in Japanese hands (Cruickshank, 1946; Hibbs, 1946; Walters, Rossiter and Lehmann, 1947).

Epidemic dropsy. Epidemic dropsy was separated from beriberi on clinical grounds in the late 1870's (O'Brien, 1879; McLeod, 1881) and now has a rich literature of its own, to which only the most scanty reference can be made. As its name implies, the disease appears in epidemics that vary in location, intensity, and character from year to year. It seems to be commonest in Calcutta and Bengal. It is not necessarily a disease of the very poor, but is largely confined to communities which have rice—but not always polished rice—as their staple cereal. Children and adolescents are commonly affected (De, 1926). The disease is characterized clinically by fever, frequently by diarrhoea and sometimes by a raised blood pressure. The oedema, which is at first very firm and hard, may or may not be limited to the dependent parts, and the overlying skin is frequently erythematous. There may even be a petechial rash and localized capillary angiomata. The total serum proteins are said to be normal, but the figures given for the serum albumens and globulins by Ray (1927–8) must be regarded with suspicion. Signs of cardiac distress and dilatation are common and so is glaucoma. Biopsies of skin and post-mortem examinations show generalized capillary dilatation and hypertrophy, and perivascular infiltration with endothelial cells (Banerjee, 1926; Chopra and Bose, 1933; Chopra and Bhattacharya, 1935; Chopra and Chaudhuri, 1935; Chopra, Chaudhuri and Panja, 1935; De and Chatterjee, 1935; Kirwan, 1935; Pasricha, Lal, Malik and Biswas, 1939). For a long time the syndrome was not clearly separated from beriberi and it was thought to originate in a food deficiency of the same type. The disease has also been attributed to a virus or bacterium, to rice which contains weevils or is infected with poisonous substances, to ankylostomiasis (Bigland, 1920), and more recently to a toxic substance in the oil expressed from the seeds of *Argemone mexicana.* This plant is a common contaminating weed in mustard fields, and the seeds, which are similar in appearance to those of mustard, are harvested and crushed with them. The disease or something very like it now seems to have been produced in human volunteers by giving them experimentally contaminated mustard oil (Sarkar, 1926; Editorial, 1933, 1939; Sarkar and Gupta, 1933; Chopra, Pasricha, Goyal, Lal and Sen, 1939; Chopra, Pasricha and Banerjee, 1940; Lal, Chatterji, Agarwala and Gupta, 1941; Lal and Gupta, 1941; Mukherji and Mathur, 1941). Since, however, the syndrome seems to be somewhat protean in nature, there may very well turn out to be more than one exciting cause. Only further experimental work is likely to settle this.

The infantile syndrome. The clinical complex of malnutrition in infancy can at times give rise to oedema. Cases were seen at the siege of Paris (Vacher, 1871),

and isolated cases or small epidemics have been reported by many people (Dewolf, 1902; Chaplin, 1914; Hamburger, 1921). Von Kostyál (1935) was probably describing the same syndrome, but he does not seem to give the ages of his patients. Shukry, Mahdi and Gholmy (1938) observed 18 cases of oedema in Egyptian children. Most were between 2 and 3 years of age, but one was aged 8 and another 10. The oedema had always followed a gastro-intestinal disturbance and starvation or semistarvation for three days to two months. During the second world war, and particularly during the winter of 1941–2, there was widespread hunger in Greece, and Petrides (1948) saw more than 100 oedematous children, all of whom were over 6 months of age. Their serum proteins were subnormal and became more so as the children approached puberty. Some of these children were said to have a "pellagroid" rash and, commonly, a fine branny desquamation of the skin, but unfortunately the author gave no quantitative data about these children's diets. Véghelyi (1948) frequently saw infants with oedema in Budapest before it finally fell to the Russians towards the close of the second world war. Pitting of the hands and feet and even gross oedema have been described as a part, but not an invariable part (Benjamin, 1914; Lederer, 1914), of the syndromes of Mehlnährschaden (Czerny and Keller, 1928), kwashiorkor (Williams, 1933) and infantile pellagra (Trowell, 1939–40; Trowell and Muwazi, 1945a, b). Payne and Payne (1927) described an "edema disease" among children aged 1 to 3 in Haiti, which they considered was not due to malaria, intestinal parasites or beriberi. Waterlow (1947, 1948) has given a very full account of this syndrome as it appears in the West Indies, and a critical review of the literature which shows that infantile malnutrition with or without oedema is common all over the tropics and in South America.

Although this infantile disease or group of diseases is certainly nutritional in origin, and almost as certainly due to one or more deficiencies, there are clinical grounds for separating it from the syndrome of undernutrition in adults as it is known in Europe, and this has been done in the present review. Hottinger (Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948) might not agree with this, for he considered that severe undernutrition at all ages led to the same dry skin with hyperkeratosis, loss of muscle and fat, subnormal temperature, a slow pulse and respiration rate, and a susceptibility to infections coupled with an inability to react to them. This is all true, and the oedema is another point of resemblance, but the infantile syndrome as described by Williams (1933), Shukry *et al.* (1938), Trowell and Muwazi (1945a, b), Gillman and Gillman (1945a, b), Magalhaes *et al.* (1945–7), and Waterlow (1948) is much more complicated than the adult form. In adults the primary deficiency has always been one of Calories; in infants it may be of proteins, specific amino-acids, or vitamins. The skin lesions, for instance, have been considered to be pellagrous. The liver is often enlarged and very fatty, but in the tropical forms of the disease it may be small and cirrhotic. Waterlow (1948) regarded the changes in the liver as the most important part of the whole syndrome, but he recognized that the pathology of the pancreas might also be very significant. Recent publications have tended to support this (Magalhaes *et al.*, 1945–7; Davies, 1948; Véghelyi, 1948). In adult undernutrition, as it has been seen in Europe, atrophy of the liver has been the usual finding, and although there may be some fatty changes (Bettinger, 1921) cirrhosis has not been observed. The pancreas has always been reported to be normal (Uehlinger, see Hottinger *et al.*, 1948). The infant may be extremely anaemic, but anaemia is not usual in the adult syndrome.

Waterlow (1948) considered that the oedema in infancy was due to a lowering of the serum proteins and to a fall in the albumen/globulin ratio, but he admitted that the serum proteins were not always low. This problem has to be faced in considering hunger oedema in adults, but, in spite of the points of resemblance, the complicating factors seem to justify excluding the infantile forms from further consideration in this review. It is recognized, however, that it may turn out to have been wrong to do so when the causes of these oedemas are known, and a study of cases of oedema in older children—such as those described by Nicolaeff (1923) in the great Russian famine, by Bennett (1847) in Ireland, by Weech and Ling (1931) in China, by Shukry *et al.* (1938) in Egypt, or by Petrides (1948) in Greece—may help to bridge the gap between the adult and infant forms. The last-named's "pellagroid" rash, for instance, and the fine branny desquamation of the skin may really have been the same as the changes which are so common in undernourished adults (*McCance and Barrett*, p. 83).

Unclassifiable oedema. Apart from oedema due to beriberi, epidemic dropsy, the infantile syndrome which has just been mentioned, and true hunger oedema, which remains to be discussed, many isolated cases or epidemics of "nutritional" oedema have been described. On the evidence which is available the nature of these must in most instances remain uncertain, and the origin obscure, but, for all that, some of them are interesting and justify their being mentioned for reasons which will be apparent later. Burnett (1933) described a series of epidemics among prisoners and native troops in Sierra Leone. The outbreaks in Freetown prison had been diagnosed by Leitch (1930) as beriberi and the diets altered to provide more Calories, aneurin, and other vitamins, but the epidemics continued just the same. The food recommended by Leitch on p. 68 of his book provided over 3,500 Calories per day, about 100 g. of fat and almost the same amount of mixed protein. This diet would certainly exclude the diagnosis of hunger oedema, or of beriberi, if the prisoners really got it. Records of a high blood pressure among the troops who were affected at Wilberforce barracks suggest epidemic dropsy, but there are other points against this diagnosis. Enright (1920) gave an account of a syndrome which he termed war oedema among Turkish prisoners of war, and Bigland (1920) wrote a very thoughtful article on the same subject. These troops were undoubtedly undernourished, but most of them had had malaria and dysentery, and many were said to have had pellagra as well. Against a simple diagnosis of hunger oedema must be set the following facts: (*a*) many of the men were very anaemic, (*b*) their pulse rates were rapid, (*c*) their urines contained albumen and sometimes casts and pus as well, and (*d*) the oedema did not disappear when the patients were put to bed. Enright himself was quite uncertain about the aetiology of the oedema.

There seems to have been hunger oedema in Turkey and its territories during the first world war, but the cases described by His (1918) cannot be confidently diagnosed as such, for the oedema affected troops who were living largely on bread and olive oil and it was said to have been cured by vegetables. Many of these men were probably suffering from a deficiency of vitamin A, and it is just possible that this helped to contribute to their oedema (Madsen and Earle, 1947), but till vitamin A deficiency has been shown to produce oedema in man it is impossible to say more. Wagner (1887) wrote an article on "die sogenannte essentielle Wassersucht". Some of his cases fall into the infantile marasmic complex, but others, the case of the boy of 12, for instance, are undiagnosable. Wheeler (1902) described a most puzzling outbreak of what he thought might

be beriberi in a camp for Boer prisoners at St. Helena. There were 3,000 men in camp and their diets were said to be good. They had, as a matter of fact, exactly the same food as the troops guarding them, and it consisted of potatoes, bread, vegetables, fresh meat four days in the week, and tinned meat on two of the remaining days. There was no malaria. This can hardly have been beriberi, or epidemic dropsy. Ankylostomiasis is a possibility (Bigland, 1920; Greig, 1920; Nixon, 1920a), and this may have been at the back of the epidemic in Ceylon which was discussed by Hunter (1807), but the patients were not anaemic and did not have albuminuria.

The duty of a medical historian is not merely to repeat or record the statements and findings of others. If he is to make any contribution of value he must take the responsibility of interpreting the earlier records in the light of the knowledge that has been acquired since they were made. Most writers on the historical aspects of hunger oedema have failed to carry out this duty. Some of them have merely recopied the statements of their immediate predecessors to give a historical veneer to their reviews of the subject. Many of these oft-quoted statements are not even to be found when the originals are consulted. For example, two people searching independently have failed to discover the passage about "Wassermenschen" in Erisman's (1879) book to which reference has so frequently been made. One reason for discussing these records of unclassifiable oedemas and of epidemic dropsy is that many of them have been referred to confidently as descriptions of inanition oedema since this syndrome became widely recognized. Thus, under the title of "Nierenentzündungen im Felde" Hirsch (1916) published an article in the introductory paragraphs of which he wrote:

> In der älteren Literatur finden sich über das Auftreten von Ödemen bei Soldaten im Felde interessante, aber ätiologisch heute nicht mehr zu deutende Angaben. So berichtet de Haen, dass fast das ganze Heer Karls V. bei der Expedition gegen Tunis durch Erkältung und Überanstrengung hydropisch geworden sei. (See also Pilgerstorfer, 1948.)

At least nine or ten authors have referred to this as an early description of hunger oedema. It is clear that Hirsch did not consider it to be so, and since the campaign was very short and the army of Charles V does not seem to have been short of food except possibly for three weeks during the siege of Goletta, but to have suffered greatly from heat, thirst and dehydration (Armstrong, 1910; Brandi, 1939), it is difficult to see how the mistake came to be made or to find any excuse for its perpetuation.

German authors are particularly fond of referring to Wheeler's (1902) article as a record of hunger oedema, with the implication that the British were starving their prisoners of war. Greig's (1911, 1912) papers are also frequently alluded to by Germans as descriptions of hunger oedema, but both papers were clearly concerned with epidemic dropsy. Patterson's (1899) article on "starvation oedema" has frequently been referred to in a similar way, but his clinical descriptions show that his patients were not suffering from straightforward hunger oedema. They had been living on weeds of unknown varieties, and the eyelids, hands and neck are mentioned as sites of the oedema. The overlying skin is stated to have been dusky and in one case to have become gangrenous. His first patient was a girl of 16, an unusual age and sex for hunger oedema. These patients were unquestionably half starved, but the oedema may have been caused by a poisonous weed as it is in epidemic dropsy.

Under the title of "An edema disease in Haiti" Mann, Helm and Brown (1920) and Mann (1924) described a curious syndrome largely confined to male

native prisoners of the older age groups. It was characterized by emaciation, weakness, a slow pulse, oedema without albuminuria, diarrhoea, a subnormal temperature, and sometimes by a gnawing sensation in the region of the stomach. It is stated that the men were sometimes in a good physical state on admission and developed the disease within a short time. It is difficult to understand this, but a change from the open air of Haiti to a crowded prison may have had something to do with it (Wickersham, 1929). In 1920 good food is said to have been of little benefit, but the dietary side of this paper is rather weak. Mann considered that they were not dealing with "war" or "nutritional" oedema, but it is difficult to see what else the disease can have been, and by 1929 dietetic and hygienic reforms had almost eradicated it. Wickersham (1929), in reviewing the possible causes for the prevalence of the oedema before 1920 and its disappearance since that time, stated that vagabonds were often still admitted to prison in very poor physical condition but they did not develop oedema. By 1929, however, the general treatment of prisoners and particularly their diets had been greatly improved; the food provided 3,000 Calories per day and included meat, pork, and eggs. Wickersham considered that the disease was allied to "war" oedema and was probably due to a deficiency of protein.

THE HISTORY OF HUNGER OEDEMA

Early Records of Hunger Oedema

Although this syndrome was not widely recognized till the first world war, there are many interesting references to it in the older literature. There is a possible one in Hesiod (*c.* 700 B.C. b), for instance, where it is suggested that the man who does not take every opportunity of increasing his substance by hard work may find himself in a bad winter without means of support, pressing his swollen feet with skinny hands (Salzmann, 1948).

μή σε κακοῦ χειμῶνος ἀμηχανίη καταμάρψῃ
σὺν πενίῃ, λεπτῇ δὲ παχὺν πόδα χειρὶ πιέζῃς.

Then there is the reference to God's kindness in Nehemiah, IX, 21: "Yea, forty years didst thou sustain them in the wilderness, so that they lacked nothing; their clothes waxed not old, and their feet swelled not." It is difficult to believe that the person who invented the story about the philosopher Heraclitus was not familiar with the signs and causes of hunger oedema when he said that he became dropsical after removing himself to the mountains and living on grass and herbs (Diogenes Laertius, *c.* 300):

καὶ τέλος μισανθρωπήσας καὶ ἐκπατήσας ἐν τοῖς ὄρεσι διῃτᾶτο, ποας σιτούμενος καὶ βοτανίας. καὶ μέντοι καὶ διὰ τοῦτο περιτραπεὶς εἰς ὕδερον κατῆλθεν εἰς ἄστυ καὶ τῶν ἰατρῶν αἰνιγματωδῶς ἐπυνθάνετο εἰ δύναιντ' ἐξ ἐπομβρίας αὐχμὸν ποιῆσαι.

And a little further on there is another reference to his oedema:

σῶμα γὰρ ἀρδεύσασα κακὴ νόσος ὕδατι φέγγος
ἔσβεσεν ἐν βλεφάροις καὶ σκότον ἠγάγετο.

"A fell disease flooded his body with water, quenched the light in his eyes, and brought on darkness."

Josephus (*c.* 80) twice mentions the prevalence of hunger oedema in Jerusalem when it was besieged by the Romans:

παῖδες δὲ καὶ νεανίαι διωιδοῦντες ὥσπερ εἴδωλα κατὰ τὰς ἀγορὰς ἀνειλοῦντο

and a little later:

παρεγίνοντο μέν γὰρ ἀπὸ τῆς ἐνδείας πεφυσημένοι, καὶ ὥσπερ ὑδρωπιῶντες ἔπειτα ἀθρόως, κενοῖς ὑπερεμπιπλάμενοι τοῖς σώμασιν ἐρρήγνυντο, πλὴν τῶν δι' ἐμπειρίαν ταμιευσαμένων τὰς ὀρέξεις, καὶ κατ' ὀλίγον προθέντων τροφὴν ἀπειθισμένῳ τῷ σώματι φέρειν.

The first passage was translated by Whiston (1737) as "the children also and the young men wandered about the market-places like shadows, all swelled with the famine", but the Greek phrasing suggests that the translation should be "swollen like ghosts", and this is a reasonable remark for Josephus to have made, for ghosts were and in some places still are pictured as bodies risen from the grave and swollen from decomposition. The other interesting point about this passage is the reference to the men and boys. Josephus may have recognized that men were more liable to oedema than women, but it seems more probable that his sentence merely implies that boys and men were more likely to be about the streets. The second passage refers to the Jews who deserted. Whiston's translation is not good, but it conveys the sense and the passage must be one of the earliest references to the dangers of allowing starving people free access to food. "For when they came first to the Romans, they were puffed up by the famine, and swelled like men in a dropsy. After which, they all on the sudden overfilled those bodies, that were before empty, and so burst asunder; excepting such only as were skilful enough to restrain their appetites; and by degrees took in food into bodies unaccustomed thereto."

There was a famine in eastern France in 586 which was described by Gregorius, Episcopus Turonensis (*c.* 590). After the usual account of a search for anything such as pounded grape seeds, fern roots, and hazel catkins that would eke out the flour comes the sentence: "Fuerunt etiam multi quibus non erat aliquid farinae, qui diversas colligentes herbas et comedentes tumefacti deficiebant." "Many, who had no flour at all, plucked and ate various kinds of grass, whereupon their bodies swelled and they died" (see Gregory, Bishop of Tours, *c.* 590). There was another famine in France in 1032 in which people were described as mixing light-coloured earth with their flour in the hope of making it go a little further (Rodulfus Glaber, 1046). The passage runs: "Effodiebant enim plerique albam humum argille similem permiscentes quantum erat farine vel cantabro, exinde panes conficiebant, ut vel sic inedie mortis succurrerent; in hoc conficiendo spes tantum erat evadendi, sed profectus inanis." Then follow the interesting remarks: "Tenebat igitur pallor et macilentia ora cunctorum, cutisque distensa inflatione in plurioribus apparebat." (All had pale and wasted faces and many people seemed to have swollen, blown-up skins.)

The years 1123 and 1124 were marked by very hard winters, late springs and bad harvests over most of Europe. The Rhine was frozen in both years, and many of the poorer women and children died of the cold. In the following year (1125) there was a serious famine throughout Belgium, Westphalia, and central Germany. South Germany and Switzerland were also affected to some extent. The grain only lasted till November in Flanders and Brabant, and from then on till the new harvest the population was reduced to starvation rations and there were many deaths (Curschmann, 1900).

Qua tempestate non poterat solito more sese quisque cibo et potu sustentare, sed contra morem tantum panis insumpsit epulator semel in prandio, quantum ante hoc tempus famis in diversis diebus sumere consueverat, atque sic per insolentiam est gurgitatus, et omnes naturales receptaculorum meatus distenti nimietate repletionis cibi et potus, natura languebat. Cruditate quoque et indigestione tabescebant homines, et adhuc fame laborabant, donec spiritum exhalarent ultimum (Galbertus, 1125).

This passage seems to be an attempt to describe the effects on a starving man of an occasional heavy meal, composed mainly of some of the flour substitutes or adulterants which were in common use (see also Josephus, *c.* 80). The writer continued: "Multi quoque inflati sunt, quibus cibus et potus fastidiebat, quibus tamen utique abundabant." (Some people could not bring themselves to eat the diet although plenty of it was available, and many of these became bloated.)

The Crusaders were extremely short of food during the winter of 1190–1 when they were besieging Acre. Bad organization, bad weather, and the activities of the Turks all combined to prevent their supplies coming through by sea, and "a certain very severe disease spread among the men . . . with the excess of the affliction, their limbs becoming swollen, the whole body was affected as with the dropsy, and from the violence of the disease, the teeth of some of them were loosened and fell out" (De Vinsauf, *c.* 1192B).

Praeterea ex nimia imbrium inundatione quaedam nimium vehemens excrevit in hominibus infirmitas. Inauditae quidem pluviae, assiduae, immo continuae, exercitum tanta affecit injuria, quod ex nimia afflictione, turgentibus membris, toto corpore more distenderentur lymphatico; ex cujus morbi vehementia, dentes quoque quorundam funditus exstirpati deciderunt avulsi (De Vinsauf, *c.* 1192A).

The reference to the teeth suggests scurvy, and the disease probably was this, although a few lines further back the Crusaders are described as eating all the green grass and herbs they could find or grow since other food was so scarce. There is nothing in the experimental work on scurvy to suggest that a deficiency of ascorbic acid leads to oedema (Vitamin C Sub-Committee, 1948), but Anson (1753) described it as one of the cardinal signs of scurvy, and the association in the older literature is too common to be due to chance. Lubarsch (1921a) was convinced of it. There are two reasonable explanations, one of which was offered by Budd (1841–2). He pointed out that scurvy and emaciation were often found in one and the same person, because sailors and others, who had to live on salt beef and biscuits, found it very hard to do so when scurvy had made their gums foul and their teeth loose. This explanation probably accounts for the cases of oedema, reported by Waddell (1827), Lilienfeld (1851), and in the *Medical and Surgical History of the British Army which Served in Turkey and the Crimea* (Army Medical Department, 1858). One cannot, however, neglect the possibility that some of the Crimean cases were really due to trench foot, for Baudens (1857) makes it clear that this must have been very common in the winter of 1855. His description seems to leave no doubt about the diagnosis:

En 1855, le froid n'a pas été très intense; ce sont les pluies, qui ont abondé; le sol est resté longtemps détrempé, surtout dans les tranchées. Les pieds des soldats, macérés dans l'eau glaciale, ont subi des effets de congélation semblables à ceux que nous avions observés en 1836 sous les murs de Constantine. C'était une tuméfaction accompagnée de rougeur et de plaques gangreneuses plus ou moins prononcées.

Many of the great famines have been due to droughts—often in two successive years—and this is the second explanation for the association of scurvy and hunger oedema. Weather dry enough to prevent the development of the grain crops would certainly prevent the growth of vegetables, so that people were faced with a shortage not only of Calories but also of ascorbic acid (Nicol, 1940). In famines due to cold and wet one would not expect to find scurvy. In the Irish famine of 1846, however, it was the antiscorbutic crop which failed and the people were reduced to eating oatmeal and imported maize—Peel's brimstone, as it was sarcastically called (Nicholson, 1850). It is nevertheless strange that there were not more than enough vegetables available in a climate that must have been ideal for them.

Hecker (1844) gives a reference to what was probably hunger oedema in the sixteenth century. A French army under de Lautrec entered Italy in 1528 and after a victorious campaign laid siege to Naples. The French were very short of bread, and only fruit was available in any quantity. They cut the aqueduct into the city and by so doing flooded a large part of the country. Fevers broke out, probably malarial, and by July the besieging army was in a state of complete disorganization. "Those soldiers, who were not already confined to bed in their tents, were seen with pallid visages, swelled legs, and bloated bellies, scarcely able to crawl."

Contemporary records of the first half of the seventeenth century quoted by Lammert (1890) tell of the dreadful state to which the townsfolk of Breisach, Baden, were reduced by famine during the Thirty Years War, and this account contains the first suggestion that the intake of salt had anything to do with the production of oedema.

Die Hungersnot war so gross, dass man auch Hand an die Leichen legte. Am 10. Dezember hatten einige Bürger ihre Kinder verloren und war damit der Vermutung Raum gegeben, die armen Kleinen seien vom Hungerteufel geraubt und auf die Schlachtbank gelegt worden. Manche Leute suchten sich 4–5 Wochen lang mit warmem Wasser und Salz zu erhalten, die sind jedoch hernach Gelingen gestorben. Derselben Köpfe und Füsse sind völlig verschwollen.

Many of Bligh's men undoubtedly had hunger oedema at the conclusion of the celebrated boat voyage after the mutiny on the *Bounty*, for Bligh noted in his diary on June 10, a day or two before reaching Timor, that "an extreme weakness, swelled legs, hollow and ghastly countenances, a more than common inclination to sleep, with an apparent debility of understanding, seemed to me the melancholy presages of an approaching dissolution", and on June 14, after their arrival, that "our bodies were nothing but skin and bones, our limbs were full of sores, and we were clothed in rags" (Bligh, 1792; Irving, 1936). The only other possible diagnosis is immersion foot, but although the boat's crew had experienced very rough weather in the early part of their voyage the general evidence is against this diagnosis and in favour of hunger oedema.

Pringle (1764) is considered by Salzmann (see Hottinger *et al.*, 1948) to have given the first account of hunger oedema in the medical literature, but this is extremely doubtful. The campaigns in the Low Countries and Germany in 1742–7 were not marked by great nutritional privations and Pringle was satisfied that the troops were reasonably well fed (p. 87). His references to oedema on p. 221 suggest heart failure rather than hunger oedema, for he speaks of the accumulations of fluid being accompanied by "a paucity and thickness of urine."

There are several references to hunger oedema in the nineteenth-century literature. It must have been extremely common during the retreat from Moscow in 1812, complicated no doubt by frostbite, trench nephritis, and possibly by trench foot, but it was not even mentioned by Kerckhoffs (1814), and Holzhausen (1912) says much less about it than about the conjunctivitis from which the troops also seem to have suffered. Was this snow-blindness or could it have been due to a deficiency of vitamin A? Holzhausen does, however, note that weakness and exhaustion, often preceded by swellings of the limbs, accounted for the great majority of the deaths. Gaspard (1821) gave a magnificent description of the physiological effects of the famine which followed the heavy rains in 1816 in central and eastern France. He emphasized the oedema, amenorrhoea, and reduced conception rate which prevailed during April, May, and June of 1817, when the population was subsisting largely on green vegetables, and he pointed out that the oedema did not disappear till normal diets were restored. He added,

moreover, the significant remark that it persisted for a long time in some people in spite of the return to full rations.

The Irish regarded the appearance of oedema as a very ominous sign during the famine of 1845–6–7, and some very fine clinical observations were made at this time both in Ireland and in Flanders, where there was a winter of great hardship, distress, and poverty in 1846–7 (Mareska, 1846, 1849–50; Lebrun, 1865). The Irish famine was due to the destruction of the potato crop by blight and was accompanied by an epidemic of typhus and a great deal of diarrhoea, sometimes with ulceration of the lower bowel (McCormick, 1847; Donovan, 1848). Scurvy was also diagnosed (Editorial, 1846; McCormack, 1846), but this disease can never have been widespread, for in many parts the people were reduced to living on cabbage (Society of Friends, 1847) or on turnips, which they did not know how to grow properly (Tuke, 1847). These problems in diagnosis made the recognition of the effects of pure undernutrition more difficult (Reviewer, 1847), but in some places the epidemic of typhus came late and Halpin and Mease (1849) noted that "dysentery, diarrhoea and anasarca were very prevalent in this country [Cavan] prior to the breaking out of the epidemic of typhus fever." These two physicians also reported that the people sometimes had a very slow pulse. Many observers recognized the true relationship of oedema to undernutrition. "In laying before the governors the fourth annual report, I beg to state that dysentery and general dropsy, from debility, prevailed in this district to a great degree during the spring and summer months" (Pratt, 1848). "Some are frightfully swelled owing to their having subsisted on cabbage alone for many weeks" (St. G. Knox, see Society of Friends, 1847). "Many of those who have been living on one poor meal a day are very much swelled in their limbs and bodies" (W. A. Fisher (1846), see Society of Friends, 1847). "Some of the children were like skeletons—and their limbs wasted so that there was little left but bones" (Society of Friends, 1847). "The husbands or sons were prostrate under that horrid disease—the results of long continued famine and low living, in which first the limbs and then the body swell. . . . Perhaps the children presented the most piteous . . . spectacle. Many were too weak to stand, their little limbs attenuated—except where the frightful swellings had taken the place of previous emaciation" (Bennett, 1847). O'Rourke (1875) reported that some of the people died looking like skeletons whereas others had oedema, and that the oedema might be brought on by hard physical work. Donovan (1848) gave a graphic account of the psychological effects of famine. After describing the "frightful emaciation" of the face and limbs he noted that the eyes acquired a most peculiar stare and that some people became very emotional, crying, whining, and appearing to be in a state of imbecility. "I have seen mothers snatch food from the hands of their starving children, known a son to engage in a fatal struggle with a father for a potato, and have seen parents look on the putrid bodies of their offspring without evincing a symptom of sorrow." Sudden death during or following some activity, and many of the other phenomena which have since been described as new, were reported in Ireland at this time (Society of Friends, 1847).

Equally important observations were made in Flanders. This famine was also due to potato blight and a good deal of research was directed towards elucidating the cause (Dieudonné, Nollet, Leroy, Biver and Scheller, 1845; Janssens, Loriers, Pypers, van Camp, Verbert and Matthyssens, 1845; Mareska and Kickx, 1845; Matthys and d'Hauw, 1845; Poelman, 1847). The infecting fungus was described by Morren who also transmitted the disease to healthy

plants by inoculating them with mycelium and spores, but these excellent observations were not generally accepted, for most people regarded the fungus as a secondary invader. Mareska and Kickx, however, suggested that copper sulphate might be tried as a preventive agent. A slow pulse at rest, subnormal temperature and oedema were clearly described as some of the results of insufficient food. Women were recognized to withstand undernutrition better than men, and the complication of diarrhoea was accepted by all.

Ils avaient tous le teint pâle, blafard, terreux ou jaunâtre. Les lèvres, les parois internes de la bouche, les gencives et la conjonctive étaient décolorées. La voix était faible et le regard éteint ou sans expression. Le visage et les extrémités étaient oedématiés, ou d'une excessive maigreur comme le reste du corps. L'haleine était fétide, les selles liquides et fréquentes, la peau sèche et d'une couleur terne; l'appétit était naturel ou surexcité. . . . La respiration était lente et profonde. Le pouls, parfois fréquent, mais le plus souvent d'une lenteur excessive, était petit faible; il fuyait sous les doigts et disparaissait par la plus légère pression. La chaleur du corps était diminuée; la moindre action provoquait une gêne dans respiration et des battements du coeur. . . Les contractions musculaires et tous les mouvements étaient lents et pénibles, et à cette inertie physique se joignait l'inertie morale portée au plus haut degré (Mareska, 1849–50).

The numbers of erythrocytes were found to be somewhat below normal (see also Bourgeois, 1855), but the serum proteins were noted to be proportionally much more reduced than the red blood corpuscles. Mareska (1849–50) even suggested that the fall in the serum albumen was the cause of the oedema:

. . et l'albumine elle-même s'épuise et descend à des limites en deçà desquelles le sang devient impropre . . . à l'entretien de la vie. . . . Telle est, à nos yeux, la dyscrasie humorale qui a affecté nos pauvres, et qui s'est terminée par l'hydropisie ou le marasme, toutes les fois qu'elle a pu sans entraves continuer sa marche vers le terme fatal. . . . La diminution de l'albumine du sang une fois constatée, ce fait jette un grand jour sur la fréquence des hydropisies pendant la crise alimentaire.

The post-mortem findings in those who had died with and without oedema were also described by Mareska, and the complete absence of fat except behind the eyeball and the relative normality of all the internal organs with the exception of the gut were noted (Mareska, 1846, 1849–50; Lebrun, 1865).

There is little about hunger oedema during the siege of Paris, but it seems to have been observed (Guillermin and Guyot, 1919), and one of the *Lancet's* correspondents (1871) commented on the extreme loss of weight and polyuria, which, as will be apparent later, indicate almost the same thing. There was widespread famine with oedema in Finland between 1862 and 1868 (Sievers, 1930). Both Cornish (see Digby, 1878) and Porter (1889) reported the presence of oedema during the famine in southern India in 1876, 1877, and 1878, and Cornish commented on the fact that it tended to obscure the true loss of weight. Porter's observations were based on post-mortem material. Chevers (1886), writing soon after epidemic dropsy had first been differentiated from beriberi, gave a lucid account of the oedemas of India, and added this delightful little note on the prognosis of what was probably hunger oedema: "In 1883, I saw the report of the death of a senior brother officer, the statement of whose case I, as secretary to the Medical Board, read in 1857. He had undergone considerable hardship in the siege of Sangor, was probably rather scorbutic, and was described as being dropsical and oedematous. He subsequently resided at Cheltenham for a quarter of a century, dying at the age of 78." (Sangor was besieged for eight months during the Mutiny in 1857 and the principal crops of the district are wheat, millet, pulses, and oilseeds.)

Scott (1905) had oedema of the legs on returning from his southern explorations in the summer of 1902–3. Members of his party also had signs of scurvy, and Shackleton was a very sick man. The party which made a fifteen-day

expedition to the western mountains in the same spring, i.e. in September, also returned with "very badly swollen legs" and signs of scurvy. Scott reckoned that they had had about 1½ lb. of food per man per day on the journey (Chapter XIII), which lasted 93 days, and if this is assumed to have had the composition and water content of the rations outlined in Chapter X, these men had been having nearly 3,000 Calories per day. Their output of energy, however, must have been enormous, and they had all lost a great deal of weight and were evidently very undernourished on their return. If this be considered hunger oedema, as on fairly good grounds it may be, in spite of the complications introduced by the scurvy, then its appearance on a ration of 3,000 Calories per day containing 100 g. of fat and about 200 g. of protein has probably no parallel in the literature. Cherry-Garrard, Wilson and Bowers had oedema of the legs on returning from their winter expedition to collect emperor penguins' eggs in 1911 (Cherry-Garrard, 1922). It is impossible to summarize the privations of *The Worst Journey in the World* and very difficult to estimate how much food these men had been able to eat while they were on it. They were certainly worn out and undernourished on their return, but they had suffered terribly from cold as well as hunger, and this must be taken into account in deciding about the aetiology of the oedema (see later). Bowers's diary (quoted by Seaver, 1938) certainly suggests that there was an element of trench foot or immersion foot in this oedema. "Aug. 2nd. The sudden warmth of the hut affected all our feet, and for over a week we walked about like cats on hot bricks, the only relief being to make one's feet cold when the pain went off." When the subject of oedema was being discussed in the Antarctic in 1911–12, Wilson "was of opinion that on returning from sledge journeys" on Scott's *Discovery* expedition of 1902–3–4 "they had wrongly attributed to scurvy such symptoms as rash on the body, swollen legs and ankles, which were rather the result of excessive fatigue" (Cherry-Garrard, 1922). Wilson was a medical man and this statement is interesting in that it shows the state of knowledge about such oedemas in 1911–12. Undernutrition would have been the first diagnosis to have been suggested ten years later.

Kisskalt (1921), writing when everyone had become oedema "conscious", inferred that there had been a great deal of hunger oedema in East Prussia in 1795 because the death rate from "Wassersucht" was 4·5 per 1,000, instead of the usual range for the preceding years of 1·7–2·2, and because other evidence showed that the province had been afflicted with a severe drought the same year and an extensive failure of the harvest.

The prison literature of the eighteenth and nineteenth centuries must be considered by itself. "Many who went in healthy, are in a few months changed to emaciated, dejected objects . . . victims, I must not say to the cruelty, but I will say to the inattention of sheriffs, and gentlemen in the commission of the peace" (Howard, 1784). This pungent criticism remained true for another 100 years although there were also great improvements in that time and the careful way in which an inquiry was held into an outbreak of scurvy and diarrhoea quite early in the nineteenth century shows that the British public realized its responsibility to prisoners at that time (Penitentiary at Milbank, 1823, 1824). Prisoners were badly fed for many reasons. Bread and water—and not nearly enough of the former—made up the usual diet of the short-term prisoner and were regarded as part of the punishment. This was still true of many of the dietaries for native prisoners in the colonial territories in 1930 (Leitch, 1930).

Even if the old prison diets were sufficient on paper their monotony and the general misery of prison life were often enough to prevent prisoners taking enough of them. Food was sometimes left untouched by prisoners who were already half starved. Apart from Calorie deficiencies, moreover, diets of bread and water were bound to lead to scurvy and night blindness, if not to xerophthalmia. Indeed, the whole catering system was deplorable by modern standards, and might have been designed to promote abuse. In some prisons "the paupers and prisoners were obliged to supply themselves . . . from their own earnings"; in others they were allowed to sell their allowance of bread for spirits, and at Birmingham in the late eighteenth century the prison governors received no salary and kept themselves on their licences for beer. In many gaols "I have seen the turnkeys themselves, bloated from intemperate drinking, with tumid or ulcerated legs and large red carbunculated faces" (Good, 1795; see also Inspectors of Prisons, 1836). Small wonder that nutritional ulcers were common (Good, 1795) or that Baer's (1876) descriptions of prisoners make one of the best word pictures of undernutrition in the whole literature.

Die meisten Gefangenen—und ich denke hier vorzugsweise an Zuchthausgefangene nach einer nicht kurzen Strafzeit—sehen blass, fahl, schmutziggelb aus, aufgedunsen oder abgemagert. Sie erscheinen viel älter, als sie wirklich sind, sie schleichen stumpf und lass in ihren Äusserungen und Bewegungen dahin. Das Fettgewebe ist meist geschwunden, die Haut ist runzlich und trocken, die Muskulatur schlaff und spärlich, der Puls klein und langsam. Die Körpertemperatur ist gesunken, die Extremitäten fühlen sich kalt an, und der Gefangene selbst ist gegen Einwirkung der Kälte ausserordentlich empfindlich. Der Stoffwechsel ist gesunken und alle Organe haben ihren Tonus, ihre Energie eingebüsst. Es ist eine frühzeitige Decrepität des ganzen Organismus eingetreten.

The asylums were little better (Third Report, 1816). Since no two prisons were managed in the same way, however, generalization is difficult, and conditions seems to have been good here and there. The poorhouse at Leeds was singled out for praise by Good (1795) and Falger's (1867) article shows that the prisoners were really well cared for at Münster at that time. According to Howard (1784) the Dutch prisons were much better than the English in the latter part of the eighteenth century, but even at the end of the nineteenth century the Rate II diet for male prisoners in Scotland only provided 2,140 Calories per day, and until 1895 men were kept on such diets for periods up to 60 days (Dunlop, 1899).

There is no shortage of information about prison diets in the nineteenth century (Inspectors of Prisons, 1836; Combe, 1837; Beneke, 1853; Wald, 1857; Böhm, 1869; Voit, 1876; Cless, 1879; Baer, 1899), and a good deal has also been written about the death rates and the diseases from which prisoners suffered. The death rates were always higher among prisoners than among free men of similar age and station, and epidemics of typhus and smallpox were frequent at one time. There was a notorious outbreak of scurvy and dysentery at Milbank in the 1820's (Penitentiary at Milbank, 1823, 1824; Combe, 1837; Wald, 1857). Everything was conducive to a high death rate from tuberculosis, and it was high (Baly, 1845). According to this author dropsy was a relatively unimportant cause of death in English prisons by the middle of the last century, but hunger oedema must have been common, as Baer's (1876) article shows. It is, however, necessary to be cautious in assigning all the prison oedemas to an insufficiency of Calories. Good's (1795) turnkey probably had cirrhosis of the liver, and anaemia was said by Baer to have been very common. Nevertheless Baer recognized that most of the oedema in prisons was "oedema pauperum", and due to insufficient food. Dropsy, presumably of this type, was particularly common in

some institutions, notably in Sing Sing prison, New York, and it was rare in others (Baly, 1845). It must have been a very frequent sight in Prussian prisons before 1870, for it was said to have been the cause of half the deaths in some of them (Kisskalt, 1912).

The Years 1915–23

In nutritional literature the years 1915–23 really represent the period covered by the first world war, for it took a little time for the observations to be collected and published, and the nutrition of the population of many countries continued to deteriorate after the fighting ceased. This period, therefore, includes the civil disturbances in Mexico during 1914, 1915, and 1916, and the great Russian famine of 1921, which was due primarily to drought and secondarily to the reduction in the acreage under cultivation, which resulted from the war and the political upheavals which followed it.

The stage was now set for the discoveries of the next few years, for undernutrition was soon to become widespread, prolonged, and often severe in countries staffed with first-class medical and scientific men, and equipped with journals of international repute to receive their observations. Scientific interest in the subject of hunger oedema was awakened by the articles which began to appear in 1915. In July of that year Budzynski and Chelchowski read what must have been an excellent paper to a Medical Society at Sosnowiec. This was published soon afterwards in Polish, and a very full abstract of it in English appeared in the following year. Towards the end of the same month Rumpel (1915) published an article on oedema that may well have been due to undernutrition in the true sense of the term, but which Rumpel ascribed to recurrent fever. Four days later Strauss's paper appeared, in which an outbreak of oedema was confidently attributed to undernutrition. Strauss described the syndrome among Polish civilians, and he pointed out that "Die Hungerkrankheit ist ein Leiden, das der moderne Arzt nicht kennt, mindestens nicht der deutsche Arzt."

The "disease" next showed itself in German labour and prison camps, and by 1917 had begun to appear among the civilians in most of the large towns in central Europe. The early accounts of Strauss (1915) and of Budzynski and Chelchowski (1916) were soon followed by others (Jürgens, 1916; Knack, 1916a, b; Rumpel and Knack, 1916; Weltmann, 1916), and by 1917 the German literature was studded with such articles (Boenheim, 1917; Eppinger and Steiner, 1917; Döllner, 1917; Falta, 1917; Franke and Gottesmann, 1917; Hülse, 1917; Knack and Neumann, 1917; Maase and Zondek, 1917a, b; Maliwa, 1917; Schiff, 1917a; Verhandlungen Ärztlicher, 1917).

Some of the Germans clung to the idea that they were observing something new (Gerhartz, 1917), but Knack (1916a) and Schiff (1917a) recognized that previous wars had produced epidemic oedema, and Weltmann (1916) that oedema had accompanied famines in Russia even in times of peace. The syndrome was placed in better perspective after the war by Park (1918), Burger (1919), Determann (1919), Maase and Zondek (1920), Maver (1920), and Lusk (1921). Some masterly accounts of it, which contained many original observations, were published during the war. The descriptions tended to improve as knowledge matured, and clinical investigations with some balance experiments were carried out by von Hoesslin (1919), Hülse (1919), Kestner (1919), Schittenhelm and Schlecht (1919), Jansen (1920), and others. The best-known series of papers is perhaps that of Schittenhelm and Schlecht (1918, 1919a-e), but

the clinical and general accounts of Knack (1916a), Rumpel and Knack (1916), Strauss (1916), Falta (1917), Hülse (1917), Knack and Neumann (1917), Maase and Zondek (1917a, b), Schiff (1917a), Jansen (1918a, b; 1919), Park (1918), Petenyi (1918), and Lewy (1919), are all worth reading. Paltauf (1917), Hülse (1918a; 1919), Park (1918), Oberndorfer (1918), Mathias (1919a, b), Prym (1919–20; 1921), Bettinger (1921), and Lubarsch (1921a, b) ably described the post-mortem appearances and pathological anatomy, and between them made many most important observations. Burger's (1919, 1920), Jansen's (1920), or Maase and Zondek's (1920) reviews are also valuable, for the first contains a bibliography of 118 references, practically all with titles, and the last two a number of references to early German descriptions of the syndrome. The literature was again reviewed by Nonnenbruch in 1926.

The disease, as these men saw it,—for on the whole they regarded it as a disease —was one to arrest attention. Among the civilians it was at its worst in the early summer of 1917 when potatoes became very scarce, and began to improve in August when garden produce and the new crops became available. The patients were pale and the greyish-yellow tint of their faces was described over and over again in very much the same words: "Die Haut des Gesichtes ist fahl, häufig mit einem Stich ins Gelbliche"; "Porzellanartig weissgelb" is another phrase which was applied several times to their complexions. They complained of general weakness, giddiness, pains in the limbs, swelling of the lower extremities and more rarely of the face. Their pulses were slow, but this was not always obvious till they had been in bed for a little time, for slight exertion tended to raise the pulse rate considerably. Their temperatures were normal or subnormal. They had polyuria, particularly at night, and a number of authors regarded the combination of oedema, polyuria and a slow pulse as constituting a diagnostic triad. Anyone might be a victim of the "Wassersucht", but the older people were affected first and men more commonly than women. The latter finding was attributed to the fact that, although men were known to have greater food requirements than women, the rations for the two sexes were the same. The oedema was induced or exaggerated by exercise, and generally subsided spontaneously when the sufferers were put to bed, and its disappearance was accompanied by the passage of large volumes of urine which tended to have a high specific gravity and to contain much salt. In old people the diuresis did not always start for a day or two, or until some diuretic had been given, and this was attributed to coincident disease of the heart.

On examination the patients were always thin and wasted, but their loss of weight was often masked by the fluid which had accumulated in their bodies. The thinness of the chest wall altered the percussion note and the sounds heard through the stethoscope were unfamiliar. The heart was difficult to delineate, and some thought there was some evidence of left ventricular hypertrophy, but radiologically it was of normal form and size. The blood pressure varied in the usual way with age, but tended to be lower at all ages than had commonly been found. Civilians of the older age groups rarely had systolic pressures of over 180, and 140 was a more customary figure. The systolic pressures of younger men were sometimes below 100 mm. Hg and seldom over 120, and their diastolic pressures were said to be only 10 to 20 mm. Hg below their systolic. Some attributed these findings to a weakness of the heart muscle. The response of the heart to atropine was disputed (Schittenhelm and Schlecht,1918; Moritz, 1919), but it was considered to be normal to adrenaline. The capillaries were normal, so far as could be ascertained from a study of the skin and of the

nail-beds. There were no abnormal findings in the abdomen or in the abdominal organs. The livers were not enlarged, and the urine contained no albumen or other pathological substances. The non-protein nitrogen in the blood was not higher than it should have been. The kidney responded normally to the ingestion of 1,200 c.c. of water, and, it was also said, to the ingestion of salt, and when the oedema had subsided the specific gravity of the urine was high if fluids had been withheld. Opinion was divided about the incidence and importance of diarrhoea; some observers did not meet with it at all, others regarded it as a prominent feature. The nervous system was entirely normal except possibly for some tenderness over the nerve trunks. The deep reflexes were usually sluggish. Pressure over the tibia was often painful. Few of the general accounts included any discussion of the oxygen consumption and the basal metabolic rates, but by the end of the war the energy exchanges and the basal metabolic rates were known to be subnormal. The original observations were made by Loewy and Zuntz (1916), and concerned the effects of undernutrition, quite apart from oedema, on the metabolic rate (Zuntz and Loewy, 1918). In spite of their pale appearance the patients were not very anaemic. The colour index of their blood was reported to be 0·8–1·0 by some observers and over 1 by others. A relative increase of lymphocytes and of large mononuclear cells was recorded and remarked upon by several people. The percentage of proteins in the serum was as a rule, but not invariably, below the normal range. Patients occasionally lapsed unexpectedly into a coma from which they did not recover, or died suddenly from what appeared to be heart failure, but few uncomplicated post mortems were obtained. Those that were revealed an absence of the usual fat depots and a reduction in the weight of most organs including the heart. Some pathologists found the suprarenals enlarged. Histologically the kidneys sometimes showed fatty changes and the cardiac muscle a brown atrophy, but little else abnormal was discovered.

The aetiology of the new syndrome was debated for a time. When the disease first appeared it was associated with typhus, diarrhoea, and recurrent fever, and its connexion with undernutrition was not at first generally recognized. Some thought it might be caused by the diarrhoea or the recurrent fever, others suggested that the newly discovered vitamin B might be involved, and a few that it was really a form of nephritis. By 1917 or 1918, however, these views had mostly been discarded and the consensus of opinion was that the whole syndrome was connected with a deficiency of Calories and protein. It was recognized that a syndrome, identical with the new one in all respects but for the absence of dropsy, did exist, but the public and the medical profession were so impressed by the oedema that most of them forgot about the importance of considering the undernutrition. The names for the syndrome, Kriegsödem, Wassersucht, Ödemkrankheit, show this, and the fact that the "dry" cases were described as examples, of "Ödemkrankheit ohne Ödem" confirms it. By 1920 Jansen had realized that Kriegsödem was not a disease *sui generis*, but felt it necessary to make this clear and accordingly spoke of it as "das Endglied in der Kette der Ernährungsschäden". The immediate cause of the oedema was never satisfactorily settled. The intake of salt, circulatory disturbances, abnormalities of the capillaries, perhaps induced or accentuated by malnutrition or by cold, and the low serum proteins were all suggested, but none of these explanations found universal favour.

This work was all very sound and may be regarded as a product worthy of the Golden Age of German medicine, but many of the findings were not new and

the earlier papers were no better than, if as good as, the Mexican articles which appeared about the same time. Landa's (1916) description of the syndrome of undernutrition displayed a balance and a historical perspective which it would be difficult to find equalled by any of the contemporary European writers. For example, he recognized that the syndrome appeared "en epoca de carestia, de privacianes, de hambre, causadas por la guerra. . . ." His cases were complicated by alcoholism, and the inevitable diarrhoea, but he, like others, noted the preponderance of elderly men among the sufferers and the absence of albuminuria, and he summarized the clinical features as "anasarca, palidez profunda, hipotermia, bradicardia, astenia cardiaca, miastenia, dolores musculares, parestesias y disminucion o abolicion de les reflejos tendinosos". He described the heart as showing brown atrophy after death and he considered the syndrome as "una verdadera hydropesia caquectica, debida a la inanicion parcial por insuficiencia de alimentos".

The soundness of the German work was also marred by what may seem a small point, but it is one which has had a considerable influence upon subsequent thought. As already stated, most of the authors overemphasized the importance of oedema and failed to grasp its relation to undernutrition. It is true that Falta (1917) always held that the "Ödembereitschaft" was the important thing: "Die bei chronischer Unterernährung bestehende Ödembereitschaft durch den Genuss einer aussergewöhnlich wasser- und salzreichen Kost manifest wird"; and Schittenhelm and Schlecht (1919c) were even more explicit: "Die klinische Symptomatologie der Ödemkrankheit zeigt, dass man es hier mit einer Änderung des gesamten Organismus zu tun hat, und dass die Ödeme nur als Einzelsymptome zu bewerten sind." Nevertheless, for most of them it was the "Ödem" part of the "Ödemkrankheit" that mattered. They did not realize that their clinical descriptions, the results of their investigations and their post-mortem findings were characteristic of undernutrition, and that the oedema was only one of the many signs of it. This was the more remarkable since there was already a rich literature on undernutrition, much of it in their own language, and most of it available to them (Chossat, 1843; Mareska, 1846; Bennett, 1847; Society of Friends, 1847; Donovan, 1848; Lebrun, 1865; O'Rourke, 1875; Baer, 1876, 1899; Voit, 1876; Mühlmann, 1899; Roger and Josué, 1900a, b; Benedict, 1907; Roger, 1907; Lipschütz, 1911, 1915; Kisskalt, 1912; Benedict, Miles, Roth and Smith, 1919; etc. etc., and see Morgulis, 1923a, b).

Studies of Oedema between the Two Wars

With the restoration of food supplies and a more or less ordered economy to central Europe the problem of nutritional oedema faded into the background. Rumpel and Knack had realized in 1916 that this would happen, "Die Hauptarbeit muss dann der experimentellen Medizin zufallen, da die Klinik unter normalen hygienischen Verhältnissen kaum Gelegenheit haben wird, von neuem ähnliche Krankheitsbilder zu sehen." Two years later Denton and Kohmann (1918) paved the way for an experimental study by producing oedema in rats by feeding them on a diet that consisted largely of carrots (Kohmann, 1920; Maver, 1920). Such a diet must have been deficient in protein and Calories and was thought to be a reasonable reproduction of that available among starving communities. Harden and Zilva (1919) also succeeded in producing oedema experimentally in a monkey. The diet consisted largely of polished rice, Marmite, and lemon juice, and was deficient in vitamin A, but the emaciation, oedema, absence of albuminuria, and terminal diarrhoea all suggest that the authors

were dealing with hunger oedema. The effects of a vitamin A deficiency cannot, however, be completely disregarded (Madsen and Earle, 1947).

In spite of the great Russian famine of 1921–2, which was well described from the medical, social, and political angles by Mühlens (1923a, b) and Fisher (1927), the atmosphere of the 1920's was not conducive to such studies, and the experimental work which was carried out on oedema at that time was largely inspired by an interest in hospital disease or fundamental principles (Peters, 1935). Papers were published on the clinical and epidemiological aspects of epidemic dropsy, and the infantile syndrome was well described (*vide supra*), but these articles added little to knowledge about the aetiology of hunger oedema. In 1929, however, Frisch, Mendel and Peters confirmed Denton and Kohmann's (1918) work, and they made the significant observation that, although the carrot diet reduced the serum proteins of all rats, only a proportion of those so fed developed oedema. This was all reconfirmed by Luckner (1938) and might have been predicted from the publications of Starling (1909) and even of Ranvier (see Annotation, 1870) and Cohnheim (1889), all of whom pointed out that a single noxa rarely produced oedema in normal persons or animals. Lowering the serum proteins, for instance, could only be expected to produce oedema in all the animals in an experiment if the lowering was extreme. Bloomfield's (1933) critical paper introduced some uncertainty into all the work which had been done up to that time on the experimental production of oedema by this method. He did not find that a diet which was low in proteins but adequate in Calories and vitamins led to a large fall in the serum proteins of rats. There was a small fall from 6·25 to 5·35 per cent in the first 10 days but no further decrease in 21 weeks. Large numbers of animals were used and none became oedematous.

These initial changes of undernutrition were studied experimentally in man by Cutting and Cutter (1934–5), who actually found the serum proteins to have increased in these short-term experiments, although a simultaneous fall in the plasma volume had slightly reduced the quantity of circulating protein. Luckner (1938) and Luckner and Scriba (1938) found that they could cure the oedema in their rats by giving them casein or cystine, and this suggests that cystine was the limiting factor in plasma protein production, as it probably was in some of the experiments discussed by Madden and Whipple (1940). This does not prove that cystine would benefit hunger oedema in man, in whom the limiting factor may be something quite different.

Although Starling (1909) and Cohnheim (1889) had made outstanding contributions to our fundamental knowledge of oedema, its appearance before the first world war was generally taken to indicate disease of the kidneys or failure of the heart. The work done on nutritional oedema during the war modified this outlook, but Epstein (1917) was probably the first to apply Starling's principles to clinical material, and a great part of the work carried out between the wars turned on the proof or disproof of Starling's theory that lowering the serum proteins would lead to oedema by virtue of the fact that it lowered the colloidal osmotic pressure of the serum and so upset the equilibrium between the fluid in the vessels and in the tissue spaces (Weech and Ling, 1931; Peters, 1935; Weech, 1938–9). Govaerts (1924, 1925, 1927) and Schade and Claussen (1924) simultaneously developed micro-methods for measuring the colloidal osmotic pressure and these were modified and further applied by Verney (1926), von Farkas (1926), and Cope (1928–9). It was recognized that albumen was of much greater importance in regulating the osmotic pressure than globulin because its

molecule was smaller and its concentration in the plasma normally higher. The determination of the two proteins separately became an essential step in any study which set out to relate oedema to the level of plasma proteins (Moore and van Slyke, 1930), and several formulae were developed relating colloidal osmotic pressure with the percentages of albumen and globulin (Wells, Youmans and Miller, 1933; Wies and Peters, 1937; Myers and Muntwyler, 1940).

Ling (1931) showed that men coming to Peiping from the famine areas with oedema had low concentrations of albumen in their sera, and that the normal relationships of the serum proteins could be restored by a good diet. Liu, Chu, Wang and Chung (1932) made some dietary experiments on a young man and a boy who were recovering from undernutrition, complicated by hookworm infestations and diarrhoea. A protein-free diet led to a return of the oedema, which is interesting, but the apparent advantages of animal over vegetable protein in setting up positive nitrogen balances and in removing oedema may have been due to the order in which the experiments were carried out. A number of careful clinical studies were made by Peters and his associates at New Haven (Bruckman and Peters, 1930; Bruckman, D'Esopo and Peters, 1930; Peters, Bruckman, Eisenman, Hald and Wakeman, 1931, 1932; Payne and Peters, 1932). This work suggested that the level of albumen in the plasma was an important factor in the genesis of clinical oedema. If malnutrition or losses in the urine lowered the albumen below 3 per cent patients tended to become oedematous. Weech and Ling (1931) put the level a little lower—2·5–2·9 per cent. The level of globulin was of little importance and this fraction of the serum proteins might be raised by an infection or for some other reason in a patient with a low serum albumen and oedema. These workers, however, were forced to recognize one difficulty, namely that a patient with heart failure or acute nephritis might become oedematous when his serum albumen and globulin were strictly within their normal limits. Similar observations were made by others (Moore and van Slyke, 1930; Wiener and Wiener, 1930; Muntwyler, Way, Binns and Myers, 1933; Myers and Muntwyler, 1940). Youmans, Bell, Donley and Frank (1932, 1933), moreover, described an interesting form of oedema in Tennessee, which had a seasonal (spring) incidence and which they regarded as nutritional in origin, i.e. due to a deficiency of Calories and protein. The plasma proteins, however, were not on the whole low, and their level was not correlated with the degree of oedema. There was a slight correlation, however, between the degree of oedema and the level of plasma albumen. The patients did not have the slow pulse rates, low blood pressures, or low basal metabolic rates which had been such features of the syndrome in central Europe. The authors were at a loss to explain the oedema and found their results difficult to reconcile with current thought. Von Kostyál (1935) found no strict correlation between the level of plasma proteins in children and the degree of their oedema, but some of his technical methods were almost certainly faulty and his paper is not an impressive one. Kylin (1930) and Loeb, Atchley, Richards, Benedict and Driscoll (1932) pointed out another difficulty, which must be familiar to anyone who has made a careful study of nephrotic oedema. Patients suffering from this disease may develop an extensive diuresis and lose all their oedema without any change in the level of their serum protein after fever or after some obscure reorganization of their internal metabolism.

Considerations such as these made it clear that factors other than the level of serum albumen must be involved in the production of oedema. One was the intake of salt, and studies of this variable had already made considerable

progress (Hülse, 1918b; Jansen, 1918a; Maase and Zondek, 1920; Moore and van Slyke, 1930). Among others, Weech and Ling (1931) and Youmans (1932) demonstrated the importance of this second noxa by showing that oedema could be induced by adding sodium chloride or bicarbonate to their patients' diets. Further knowledge was soon acquired by the discovery of a suitable experimental animal. Leiter (1931) and Shelburne and Egloff (1931) lowered the serum proteins of dogs by plasmapheresis. The former found that the animals began to get oedema when the serum proteins had fallen to about 3 per cent, and the experiments of Darrow, Hopper and Cary (1932) confirmed this figure. The latter noted that oedema could be made to appear or disappear at this level of serum proteins by increasing or decreasing the amount of salt in the diet. Weech, Snelling and Goettsch (1933) agreed that lowering the plasma proteins alone did not lead to oedema unless the diet contained a sufficient amount of salt. Shelburne (1934) found it impossible to produce oedema in some dogs when the serum proteins had been reduced by diet alone, even when he pushed the intake of water and salt. Weech extended this work with Goettsch and Reeves (1935a, b). By feeding dogs on a mixture of carrots, rice, lard, cod-liver oil, and a salt mixture, these authors lowered the serum proteins of young adult animals to a level at which most became oedematous after a period of one to three months. They made several important observations. One was that there was no sudden acquisition of weight with the appearance of the oedema, but that there was a progressive replacement of body protein—or cell substance—by tissue fluid as the animals lost weight. This was first recorded by Bischoff and Voit (1860) and is a finding of great significance to all interested in the aetiology of hunger oedema. Weech *et al.* noted also that even when the intake of salt was controlled the level of plasma albumen at which oedema began to develop might vary from 1·04 to 2·17 per cent, so that yet other factors must be involved.

Some of these factors were undergoing active investigation at that time and some had been studied long before. The most important work was concerned with the following subjects. (1) The effect of posture on the venous pressure, the circulation time, the blood volume and the concentration of serum proteins (Böhme, 1911; Florkin, Edwards and Dill, 1930; Turner, Newton and Haynes, 1930; Youmans, Wells, Donley and Miller, 1934; Keys and Butt, 1939). (2) The effect of venous pressure on the formation of tissue fluid (Drury and Jones, 1927; Krogh, Landis and Turner, 1932; Landis, Jonas, Angevine and Erb, 1932; Looke, 1935–7). (3) The effect of varicose veins on the venous pressure and the formation of tissue fluid in the leg (Beecher, 1937; Holling, Beecher and Linton, 1938). (4) The measurement of subcutaneous, intracutaneous and intramusclar tissue pressures, and the effect of these pressures on the formation of tissue fluid (Bönniger, 1905; Holland and Meyer, 1932; Meyer and Holland, 1932; Burch and Sodeman, 1937; Wells, Youmans and Miller, 1938). (5) The permeability of the capillaries in normal and nephritic subjects (Smirk, 1935–6a, b). (6) The lymph flow in normal and oedematous limbs (Weech, Goettsch and Reeves, 1934). Most of these experiments were made on human subjects. They form an important part of the work done between the two wars on the aetiology of oedema, but a discussion of the results and their implications will be postponed till the causation of hunger oedema is under consideration.

The Period Covered by the Second World War

During the Spanish civil war the inhabitants of Madrid were on starvation rations for some time and there was inevitably an outbreak of oedema. This was

studied by Jiménez-Diaz, Roda, Mendoza, de Landázuri, Lorente and Marina (1942). The German occupation of Belgium and France was quickly followed by undernutrition and oedema (Dumont, 1941; Durand, 1942; Nicaud, Rouault and Fuchs, 1942; Martin and Demole, 1943). Beaussart, Feuillet and Secques (1943) noticed their first cases at the end of 1940 in a psychiatric hospital in Villejuif, and in the next year or two many papers were read to medical societies all over France dealing with various aspects of the syndrome (Mauriac, Laval, Monmayou and Leger, 1941; Mauriac, Broustet, Baron, Leger and Faure, 1942; Merklen and Turiaf, 1943). Many of the French and Belgian papers of this time were based upon the study of asylum inmates (Gounelle, Bachet, Sassier and Marche, 1941; Gounelle, Bachet and Marche, 1943; Leulier, Revol and Trouillas, 1942), prisoners (Simonart, 1941, 1942, 1945), people who had been thrown out of work (Duvoir, Poumeau-Delille, Durupt and Hadengue, 1942) or who had recently been in concentration camps (Loeper, Varay and Mende, 1942a), and it is not clear from this work to what extent the population as a whole was affected. Most seem to have suffered to some extent (Merklen and Turiaf, 1943; Trémolières, 1947). Accounts were published of some very typical cases (Laroche, Bompard and Trémolières, 1941; Girard, Louyot and Verain, 1942; Leulier *et al.*, 1942; Warembourg, Poiteau and Biserte, 1942; Baridon, 1943), highly reminiscent of those so ably described 20 to 25 years before, and yet Giraud, Bert and Desmonts (1942) made the surprising claim that the food conditions in certain places "entrainent l'apparition de syndromes cliniques nouveaux, parmi lesquels les plus fréquents semblent être les oedèmes et les polyuries".

It is safe to say that most of these papers added little to knowledge. It is also true, however, that the French are masters of clinical description, and some of their phrases were very apt. Mauriac *et al.* (1942) described their subjects' appetites as being so voracious that they would eat "n'importe quoi, préparé n'importe comment". Following Hippocrates (*c.* 450 B.C.) the French stressed the effects of age and sex on some of the stigmata of undernutrition (Godlewski, 1944; Justin-Besançon, 1942, 1946, 1947) and they made an interesting claim that hypoglycaemia was a cause of coma, collapse, and death in people who were seriously undernourished (Gounelle, Marche, Bachet and Digo, 1942; Lhermitte and Sigwald, 1942; Bellier, 1943; Levrat and Roche, 1943; Levrat, Roche and Bellier, 1943; Levrat, 1944). As a matter of fact, this discovery requires to be carefully confirmed by therapeutic tests, for it is well known that the blood sugar may fall to very low levels in undernutrition without giving rise to any symptoms or signs (Chakrabarty, 1948). As in 1918, however, interest for most people centred on the oedema or its removal by treatment (Gounelle, Bachet and Marche, 1943). "During the early part of the war, the dominant form of malnutrition was hunger oedema" (Bigwood, 1947). This statement reflects the twist which the clinical investigators in Germany had given to the whole subject of undernutrition during and after the first world war. It would never have been made at all prior to 1915, and it would only have been made subsequently by one whose interests were almost entirely confined to human nutrition, for animals other than man do not readily become oedematous when they are undernourished. To make so much of the association of oedema with undernutrition is to concentrate on a peculiarity of the human species, but the epidemic diseases of mediaeval famines were now eliminated, and Loeper *et al.* (1942b) were to some extent right when they stated, "De ces troubles et de ces accidents de carence l'oedème est certes le plus frappant, pourrait-on-dire, le plus spectaculaire."

Holland fared better than Belgium and France at first (Dols and van Arcken, 1944–6), but when communications broke down in the final winter of the war the ration cards only entitled a normal consumer to purchase 500 Calories per day, and the Dutch were reduced to eating sorrel, sugar beet, beech mast, tulip and even iris bulbs (Burger, Sandstead and Drummond, 1945; van Schaik, 1944–6). Of the large towns Rotterdam was probably most short of food, but everyone in western Holland suffered severely. All the classical signs of undernutrition appeared; osteopathies were observed, oedema was widespread in all the cities, and many died (Cardozo and Eggink, 1946; Banning, 1947; Bok, 1949). Nevertheless, at no time was the plight of the population nearly so bad as it must have been in many of the towns in Europe during the Middle Ages or in some of the great Indian, Chinese, and Russian famines of the nineteenth and twentieth centuries.

Many of the inmates of the concentration camps in Germany were starved to death, and in these camps conditions towards the end of the war must have been comparable with those in a mediaeval siege. Only a fraction of the men and women who lived and died in these camps were seen by Allied personnel, and most of them were seen at a time when scientific observation was difficult (Lipscomb, 1945; Mollison, 1946). After the war was over Wellers and Waitz (1947) published an interesting account of Auschwitz III and their work in the hospital there. Much of their medical and biochemical data is valuable, but their figures for the concentrations of calcium and other minerals in serum can scarcely be correct. Other medically qualified internees wrote up their experiences, unfortunately largely from memory (Adelsberger, 1946; Rosencher, 1946; Wolff-Eisner, 1947), and a few of the people from these camps were investigated in good hospitals by Hottinger *et al.* (1948), Lamy, Lamotte and Lamotte-Barillon (1946a–f), and Schwarz (1945). A number of the points made by Wolff-Eisner have been criticized, probably with justification (Anon., 1948; Oravec, 1948), but the general evidence submitted by these investigators about the camps shows that oedema was not the most arresting manifestation of the later stages of undernutrition. Only some of the people examined by Lipscomb or Mollison, for instance, had any oedema; Wolff-Eisner says little about it; 6 out of the 40 men examined by Lamy *et al.* had never had oedema, and others had none on admission to hospital. Schwarz was very impressed by the oedema in some of his cases, but others died without it. Hottinger *et al.* obtained evidence of past or present oedema in all their subjects, but they frequently had to rely for this upon the history. Oedema was there—as it always is in the presence of serious undernutrition—but the pallor, the skin disease, the loss of weight, the frequency, incontinence, and diarrhoea (Thaysen and Thaysen, 1949), to say nothing of the overcrowding, the vermin, and the utter misery of it all, were much more arresting (Lipscomb, 1945). Laycock (1944) reported on some men who had been in Japanese concentration camps. They were all in an advanced stage of undernutrition and many had lost their appetites, but as was usual in the Far East their diets had been short of aneurin as well as Calories, for their scanty rations of rice had been cooked in alkali. They were all oedematous and this oedema may have been due to simple inanition without vitamin deficiencies, for although they had no neurological signs of vitamin B deficiencies they had persistent albuminuria, and Laycock regarded them as cases of wet beriberi. The Germans did not provide adequate rations for their prisoners of war, and the Russians, who received no Red Cross parcels, suffered very severely in consequence. Leyton (1946) presented a study of the

effects of prolonged undernutrition in such men, which was more valuable than many others in that he was able to provide control subjects for most of his investigations from the British personnel who were also inmates of the camp for prisoners of war at Tost, and whose food parcels provided them with 1,000 additional Calories a day.

The Germans did not suffer from undernutrition during the war, but in the disorganization that followed it the supply of food to the Western Zones presented many obstacles. The official rations for the normal consumer dropped for a time to 1,000 Calories a day, and there were times when bread could only be obtained with great difficulty. These rations, however, never represented the whole of the food available for consumption, and the population as a whole was never in a state bordering on starvation, although there was a considerable amount of undernutrition in the towns in the spring and summer of 1946, particularly among those who had no supplies outside the official rations, or those who were too old and infirm to stand in the queues. As usual, also, the members of closed institutions such as the prisons, asylums, and internment camps suffered most, but their greater needs were soon recognized and met by issues of extra rations. There were many cases of oedema in the prisons and among the vulnerable sections of the general population, and there is no doubt that the children at this time were below the standards set up for height and weight by their English and American counterparts (Davidson, Wilcke, Fein and Reiner, 1947; *McCance and Widdowson*, p. 1). A number of articles were published on various aspects of the subject by German clinicians (Bansi, 1946a, b, 1949; Heilmeyer, 1946). There were exceptions (Landes, 1943; Landes and Arnold, 1947), but on the whole these articles did not break new ground (Heilmann, 1946; von Kress and Langecker, 1946; Markoff, 1946; Schäfer, 1946; Strauzenberg, 1946; Wilbrandt, 1946; Herrlich, 1947; Koch and Lübbers, 1947). It must be remembered that they were mostly written by men who had been deprived for years of the criticism, help, and stimulation of the international literature, and who were working in a difficult political atmosphere. The authors generally began with a review of the older German work and approached their subject from that angle. Some of the reviews were, up to a point, good (Schulten, 1946), but the ductless glands were invoked to explain the symptoms too freely and too vaguely for the explanation to be convincing, and there was an absence of quantitative thinking about the articles on "Mangelfettsucht" (Bansi, 1947; Overzier, 1948; Thienhaus, 1948) and the effects of undernutrition on children (Brock, 1946) that was not in the best German tradition. Few of the observations indeed were made under the rigid experimental discipline which clinical science has come to demand, but this is a criticism which applies equally to much of the French work (Gilbert-Dreyfus, 1948).

Keys, Taylor, Mickelsen and Henschel (1946) produced hunger oedema in a number of their volunteers, but the results of these experiments and of those described in certain other papers which have appeared since the end of the war will be discussed when the aetiology of hunger oedema is being considered.

The workers during the first world war had established that oedema frequently accompanied undernutrition and was also often associated with a fall in the concentrations of serum proteins (Rumpel—see Aerztlicher Verein, 1917; Jansen, 1918b; Schittenhelm and Schlecht, 1918). In spite of exceptions which have already been discussed, the work done between the wars left most people with the feeling that this association was really one of cause and effect. Schittenhelm and Schlecht (1919c), however, had pointed out that the association was

by no means invariable, and that the serum proteins might be quite normal in persons with oedema and very low in others who had no oedema. These observations were amply confirmed between 1939 and 1946. General agreement was soon reached that the greater the amount of clinical oedema the lower the level of serum proteins was likely to be (Beaussart *et al.*, 1943; Dumas, 1943; Raynaud and Laroche, 1943; Mitchell and Black, 1946; Mollison, 1946; van Oven, 1946; Denz, 1947), but individual exceptions were so numerous that they overshadowed the whole picture (Jiménez-Diaz *et al.*, 1942), and it was soon clear that no close association between the severity of the oedema and the level of plasma proteins was to be expected (Loeper *et al.*, 1942a, b; Warembourg *et al.*, 1942; Keys *et al.*, 1946). Furthermore, many people were observed to retain their oedema long after they had started to eat good food once more and had regained their lost weight (Gounelle, Bachet and Marche, 1942b; Jiménez-Diaz *et al.*, 1942; Denz, 1947; Ratschow and Marx, 1947; Ströder, 1947). Many investigators, however, like Youmans *et al.* (1932, 1933), found this difficult to accept and tried to find some correlation by substituting albumen for total protein (Gounelle, Sassier, Marche and Bachet, 1941; Gounelle, Marche and Bachet, 1942a, c; Dumas, 1943; Annotation, 1946).

Gounelle and his associates (Gounelle, Bachet, Sassier and Marche, 1941; Gounelle, Sassier, Marche and Bachet, 1941; Gounelle, Raoul and Marche, 1941; Gounelle, Bachet and Marche, 1942a; Gounelle, Marche and Bachet, 1942a, c) found the serum proteins within normal limits until the oedema began to appear. If the percentage of globulin was a little low at this stage, the albumen/globulin ratios might be very high. As the oedema developed the concentration of serum albumen fell whereas that of the globulin fell little if at all, and might even rise, so that the albumen/globulin ratios at this later stage were characteristically very low. In the opinion of the authors the persons with oedema always had a low concentration of albumen in their serum, but it was futile to make the extent of the oedema the basis of any prediction about the level of albumen to be found in the serum of a particular case (see also Denz, 1947). Most of these French findings have been criticized by Swiss workers (Gsell and Uehlinger, 1948) and were probably due to technical faults in the separation and subsequent determination of the serum proteins, for these operations present greater difficulties than many people have realized.

Govaerts and Grégoire (1941) measured the colloidal osmotic pressure of the serum of persons with oedema and claimed that it was lower than the pressure calculated from the percentage of albumen and globulin found in the serum: "L'hypoprotéinémie est donc la règle dans l'oedème de carence; elle n'affecte toute fois qu'un parallélisme grossier avec la pression osmotique des protéines, directement mesurée." This finding offered an attractive escape from the dilemma, and it was confirmed in a few cases by Lamy *et al.* (1946c, e). Florkin and Duchateau (1944) set the hypothesis on a chemical basis by claiming to have detected abnormal amino-acid ratios in the molecules of serum proteins in undernourished people and animals. Berning (1943) and Kühnau (1946) found that in undernutrition the serum proteins contained subnormal amounts of cystine and tyrosin and Herken and Remmer (1947) made similar but less specific claims. These claims should be regarded as variants of those of Alving and Mirsky (1936), Goettsch and Reeves (1936), Luetscher (1939, 1940), Faber (1943a, b), and Hoch-Ligeti and Hoch (1948), who have all produced evidence that the serum proteins in patients with nephrosis may differ from those in normal persons. Precipitation reactions, chemical and enzymatic studies, and

electrophoretic measurements all suggest that the albumen fraction of the serum proteins may consist of two parts and that the quantities of these may be varied by differential loss in the urine or formation in the body. Unfortunately it has not been possible to confirm the findings either of Govaerts or of Florkin (*McCance and Widdowson*, p. 204; *Jones*, p. 211); those of Kühnau and Berning have not been put to the test, but there is nothing inherently impossible in their claim. Abnormal proteins may appear in the serum in multiple myelomatosis (Bence-Jones proteinuria) or in parenchymatous disease of the liver (Fischer, Sellei and Bretán, 1948). If the same thing happens at certain stages of inanition, serum analysis might reveal unexpected concentrations of amino-acids in the "serum" proteins (Annotation, 1948a).

THE AETIOLOGY OF HUNGER OEDEMA

The influence of the German work between 1915 and 1923 was so great that most people have continued to regard oedema as the hall-mark of undernutrition and to confuse their aetiologies. Falta (1917) considered a deficiency of Calories and protein to be the cause of the oedema, Jansen (1918a) that raising the Calorie intake by potatoes would cure the disease. Maase and Zondek (1917a) claimed to have cleared the oedema by adding 100 g. of fat per day to the poor diets. Müller (1939) put the point of view which was then current into the title of his paper, "Das Kriegsödem als Eiweissmangelzustand"; the article itself contained no original thought and was written to popularize the use of slaughter-house by-products. The French workers (Gounelle, Bachet and Marche, 1942b; Gounelle and Marche, 1943) studied the effects of vitamin supplements, sugar, casein, butter, milk, and soya meal on hunger oedema. They did not equalize the Calories and the absence or extent of the oedema at the end of the treatment was the main if not the only criterion of its success. The recent German papers have continued to emphasize the importance of a deficiency of animal protein and fat in the genesis of hunger oedema (von Kress and Langecker, 1946; Strauzenberg, 1946; Ströder, 1947), but most of the articles are really reviews of older German work.

The dominant part this played in European thought, even as late as 1947, is illustrated by an article by Bruun. After reviewing the earlier German literature this author described what appears clinically to have been an absolutely characteristic case of undernutrition with oedema in a crank who was said to have been living for some considerable time on unlimited amounts of potatoes and rye bread with an egg every morning. If the clinical description is accepted at its face value, this patient must have been lying about the amounts he had been eating, for he was clearly suffering from an insufficiency of Calories and all that it entails, but Bruun attributed his signs and symptoms entirely to a deficiency of protein! If unlimited in amount, this diet cannot have been deficient in protein, and the author seems to have forgotten that Kon and Klein (1928) maintained health and nitrogen equilibrium for 167 days on diets which consisted almost entirely of potatoes and 120 to 150 g. of fat per day—and that others had done the same before them. Even Simonart (1945), however, has claimed that beef has cured a person of his oedema in two days, and that fat has a beneficial effect apart altogether from its calorific value. Basing his therapy on the findings of Luckner (1938) and Berning (1943), Ratschow (1946) claimed that cystine would cure hunger oedema. Popular views on the causation of oedema and its serious import in undernutrition were summarized by Kühnau (1946) when he wrote, "Die Existenz unseres Volkes . . . wird erneut durch den

Eiweissmangel gefährdet". No German in 1946 quoted the article by Kruse and Hintze (1920), which was based on some dietary surveys carried out during the 1914–18 war and concluded that "der grosse Fleisch- und Fettverbrauch, den wir uns damals gönnen durften, ist weder zur Aufrechterhaltung unserer Gesundheit und Leistungsfähigkeit, noch zur Herstellung der verlorenen Kräfte nötig."

Everyone will agree that the cure for underfeeding is food. In practice a Calorie deficiency is always accompanied by a shortage of protein and generally of fat. Health can be improved by supplements of protein, fat, or carbohydrate, but a balanced diet is obviously the best (Smart, Macrae, Bastenie and Grégoire, 1948) and can lead to rapid improvements in weight and strength. Undernutrition of the type all too familiar in Europe leads to changes in the body which are still very imperfectly known, much less understood. The problem is to discover why these changes upset the equilibrium between the vessels and the tissues, for there would seem to be little doubt that the oedema which accompanies undernutrition will never be understood until its characteristics are studied and its aetiology explored in the light of fundamental principles.

Definition

Before going further it is important to define the term "oedema". The word οἰδέω from which it is derived means "I swell", and the term as used in medicine generally means an ill-defined swelling in subcutaneous or peripheral parts of the body that pits on pressure and therefore consists of fluid. These accumulations of fluid are generally in the dependent parts. Oedema is not usually taken to include collections of free fluid in the serous cavities for which the terms ascites and hydrothorax are used. The fluids that accumulate in all these places are extracellular. They consist of solutions similar in ionic composition to serum, and they are localized collections of the fluids which normally bathe the cells of the body and constitute the internal environment. In the discussion which follows, the use of the term oedema will be confined to its classical meaning, namely a visible swelling of some part of the body which pits on pressure or, as in the case of the eyelids, clearly consists of fluid. It will not be used to include ascites or hydrothorax. Since sodium is the chief inorganic ion in the fluids that lie outside the cells of the body, the term "sodium space" may be used to cover the whole of the volume of the body occupied by extracellular fluid. The term is convenient rather than exact, for some of the cells of the body contain some sodium and there are quite large concentrations of sodium in the bones.

Clinical Characteristics

There are some characteristic clinical features of hunger oedema which must be taken into account in considering its aetiology. They may be set out under the following headings:

1. The appearance of oedema is generally preceded by a considerable loss of weight. This has been noted by Govaerts and Lequime (1942), Brull and Dumont (1945), and by the early workers. Oedema, therefore, is not as a general rule one of the earliest signs of undernutrition (Leyton, 1946), but it may appear quite early in susceptible people (Lichtwitz, see Aerztlicher Verein, 1917; Schulten, 1946).

2. In a community which is short of food the people to report with oedema are characteristically men over 40 (Landa, 1916; Döllner, 1917; Knack and Neumann, 1917; Maase and Zondek, 1917a, b; Schiff, 1917a; Warembourg *et al.*, 1942; Brull and Dumont, 1945; Cardozo and Eggink, 1946). The series of

ages given by Govaerts and Lequime (1942), by van Oven (1946), or by Sinclair (1948) demonstrates this very well. However, hunger oedema is not limited to the higher age groups (Gerhartz, 1917; Baridon, 1943), for in armies and camps for prisoners of war, in which young men predominate, it may be very common (Guillermin and Guyot, 1919). Schittenhelm and Schlecht's (1919a) cases were all 19–33 years of age. Children over 5 withstand periods of undernutrition surprisingly well (Brock, 1946), in that they do not get oedema until they are more or less *in extremis*. This may be a matter of adaptation between rate of growth and plasma volume (Metcoff, Favour and Stare, 1944; Quimby, 1947), or possibly because they are shorter, and their legs are therefore not subject to so great a hydrostatic pressure. Many cases have, however, been recorded in children from time to time (Knack and Neumann, 1917; Weech and Ling, 1931; Nicolaeff, 1923; Liu, Chu, Wang and Chung, 1932; Shukry *et al.*, 1938; Petrides, 1948).

3. Men are much more commonly affected than women (Lange, 1917; Lichtwitz, see Aerztlicher Verein, 1917; Maase and Zondek, 1917a, b; Guillermin and Guyot, 1919; Govaerts and Lequime, 1942; Leulier *et al.*, 1942). It should be stressed that the appearance of oedema is only one of the many features of undernutrition which are influenced by age and sex. In an undernourished community the older men tend to be the first to suffer; young women often look remarkably well (Bansi, 1947; Lohr, 1947) and this effect of sex is apparent before puberty (Godlewski, 1944; Salzmann, see Hottinger *et al.*, 1948).

4. The oedema is always accompanied by polyuria, particularly at night. This polyuria may antedate the oedema by several months, and many people who suffer from severe nocturnal polyuria never develop oedema. These observations were first made many years ago and have frequently been confirmed (Falta, 1917; Lange, 1917; Jansen, 1918a; Schittenhelm and Schlecht, 1918, 1919a; Govaerts and Lequime, 1942; Nicaud *et al.*, 1942; Brull and Dumont, 1945; Pallister, 1947; Bansi, 1949). "La polyurie prècede l'oedème, l'accompagne, et lui survit" (Rimbaud, Serre and Duc, 1942).

5. The oedema first appears in the evenings in the dependent parts or in the mornings in the face. It is very much affected by posture (Lamy *et al.*, 1946b; Bok, 1949) and often disappears after a few days in bed. These again are old observations (Maase and Zondek, 1917a) and have been made by almost everyone interested in the subject (Jansen, 1918a; Schittenhelm and Schlecht, 1918; Mauriac *et al.*, 1941, 1942; Giraud *et al.*, 1942; Nicaud *et al.*, 1942; Martin and Demole, 1943; Denz, 1947). Most of the "cures" for hunger oedema have depended for their success upon the fact that the sufferers have usually been confined to bed while the cure was being applied. The disappearance of the oedema is marked by the passage of much water and salt (Falta and Quittner, 1917; Schittenhelm and Schlecht, 1918; Govaerts and Lequime, 1942; Leulier *et al.*, 1942; Denz, 1947; Bok, 1949).

6. Exercise makes the oedema worse (Knack and Neumann, 1917; Guillermin and Guyot, 1919; Denz, 1947) but this may be an effect of posture.

7. The oedema tends to recur (Maase and Zondek, 1917a)—"L'eau attire l'eau" as the French peasants used to say (Durand, 1942). It may wax and wane for no obvious reason (von Hoesslin, 1919); it may disappear with rest only to appear again with a return to active life (Hülse, 1918b); it may first become apparent after the patients have returned to a generous diet (Stapleton, 1946; Ströder, 1947); most characteristically of all it may persist for months or even years after all other signs of undernutrition have vanished (Jiménez-Diaz *et al.*,

1942; Bruun, 1947). This has frequently been observed in Wuppertal in 1946–8, particularly among prisoners of war who have been sent home from Russia.

8. A few authors tried to incriminate the kidneys (Sittmann and Siegert, 1916; Franke and Gottesmann, 1917, 1918), but most have agreed that there is no albuminuria. Bok (1949) sometimes found small amounts of albumen in the urine but did not imply that this indicated a renal lesion. The kidneys were shown to produce concentrated urines under the appropriate conditions (Schittenhelm and Schlecht, 1919b; *McCance*, p. 175), and if, as seems justifiable, one may neglect the claims made by Döst (1947), the patients respond normally to Volhard's water excretion test (Schittenhelm and Schlecht, 1918, 1919b; *McCance*, p. 175). Schwarz (1945), however, did not find this in patients who had been in a state of severe undernutrition, and the whole matter may have to be re-examined more critically in man in the light of the work on man and animals which has been published since the second world war. Brull and Op de Beeck (1943) and Brull (1947) perfused in parallel the kidneys of two dogs, one undernourished, the other normal. They found a much smaller blood flow, oxygen consumption, urine flow, and urine output from the undernourished kidney. Interesting though these experiments are, it is difficult to see the application of this work to man, since human undernutrition is characterized by polyuria and the blood ureas are normal. The minor histological changes in dogs' kidneys which Darrow *et al.* (1932) and Shelburne (1934) produced by undernutrition were not considered to be significant in the genesis of the oedema. By feeding rats on diets which were deficient in Calories and protein, or in protein alone, Bristol workers have produced a hypoproteinaemia and a state of nutrition in which water administered by stomach tube was found to be absorbed normally, but to be excreted more slowly than it was by healthy animals. The ability to produce a concentrated urine was also impaired. One of the diets produced gross histological lesions, which have so far had no counterpart in human undernutrition (Dicker, Heller and Hewer, 1946; Heller and Dicker, 1947; Dicker, 1948a, b). They did not resemble the micro-anatomical lesions found by Lamy *et al.* (1946f) and the latter were not confirmed by Uehlinger, who considered the whole of the evidence most carefully (see Hottinger *et al.*, 1948).

9. The heart is normal; at any rate, there is nothing to suggest that the oedema can have been due to heart failure (Govaerts and Lequime, 1942; *Howarth*, p. 238). The liver is not enlarged or tender, but was reported by Lamy *et al.* (1946f) to resemble "un foie de stase, ou un foie vasculaire".

The Passage of Fluid between the Capillaries and the Tissue Spaces

This has been considered in all its fundamental aspects by Cohnheim (1889), Bolton (1907), Starling (1909), Landis and Gibbon (1933), Peters (1935), and many other people. The equilibrium depends upon four main factors.

(*a*) *The hydrostatic pressure in the capillaries.* The blood pressure in the arteries, including presumably the arterioles opening into the capillary system, is often low in undernutrition, which should have the effect of reducing the passage of fluid into the tissues. The general capillary pressure, however, varies with the venous rather than the arterial pressure and has not yet been measured in undernourished people. The movement of fluid from the capillaries to the tissues can be increased experimentally by raising the pressure in the veins. When, for example, an arm was placed in a dependent position Böhme (1911) was able to demonstrate an increased outflow from its capillaries by measuring the concentration of proteins in blood leaving the arm, and similar observations

were made on the leg by Youmans *et al.* (1934), and on the leg and arm simultaneously by Keys and Butt (1939). Landis *et al.* (1932) showed that when the venous pressure was increased by constriction beyond 60 mm. Hg proteins began to escape freely from the vessels. The increased pressure in varicose veins has been shown to promote the formation of tissue fluid (Beecher, 1937; Holling *et al.*, 1938), but there is no evidence that undernutrition increases the hydrostatic pressure in any of these ways, so that they need not be considered at this stage in any detail. Keys *et al.* (1946) found that when their undernourished experimental subjects were lying down, the peripheral venous pressure tended to be below normal. This might be invoked to explain the ready reabsorption of fluid into the blood vessels by such persons and also their nocturnal polyuria, but it might equally well not do so if it were itself due to a diminished tissue pressure—as it may have been. It is difficult to see what effect this subnormal venous pressure might have on the outflow of fluid from the vessels in such circumstances, and further measurements in the erect attitude seem highly desirable. *Howarth* (p. 238) observed high pressures in the superior vena cava in some undernourished people (and see Bolton, 1907).

(*b*) *The permeability of the capillary walls.* This may be increased by mechanical, thermal, or chemical agents, or by malnutrition in its widest sense, e.g. by anaemia. An increase in the permeability of the capillary walls has frequently been enlisted to explain the oedema of undernutrition (Schittenhelm and Schlecht, 1918, 1919e; Determann, 1919; Lubarsch, 1921b; Hülse, 1923; Müller, 1939; Berning, 1942; Jiménez-Diaz *et al.*, 1942; Chabanier and Lobo-Onell, 1945; Lamy *et al.* 1946c, e; Strauzenberg, 1946; Lohr, 1947; Schneider, 1947). German writers have postulated more particularly that the permeability of the capillaries is increased by a reduction of plasma lipids, but Bettinger (1921) found no histological evidence that loss of fat had injured the capillaries, and Prym (1921) agreed that anatomically the small vessels were in all respects normal. Uehlinger (see Hottinger *et al.*, 1948) could not confirm the histological findings of Lubarsch (1921b), and Knack and Neumann (1917) found nothing wrong with the living capillaries of the skin. Maase and Zondek (1917b) also examined the capillaries in the nail-beds during life and could not establish any divergence from the normal.

The experimental work of Smirk (1935–6a, b) with capillary pressures strongly suggested that these small vessels were abnormally permeable in nephrosis, but the investigations reported by *McCance and Thrussell* (p. 276) showed that in undernourished people the capillaries of the forearm were not unusually permeable when the venous pressure was increased, and that they were not unusually susceptible to injury by cold. If, moreover, the capillaries were abnormally permeable in undernutrition the concentration of protein in the oedema fluids should be high (Chabanier and Lobo-Onell, 1945; Cameron, 1946; Fuhrman and Crismon, 1947; Henschel, Mickelsen, Taylor and Keys, 1947), and on the whole this has not been the experience of those who have estimated it. Schittenhelm and Schlecht (1919c) found less than 1 per cent of protein in the oedema fluids, Beaussart *et al.* (1943) 0·27, Bok (1949) 0·27, Henschel *et al.* (1947) 0·20, and Youmans *et al.* (1934) 0·32 g. per 100 c.c. Similar figures have been found in animals (Luckner, 1938; Weech *et al.*, 1935b).

(*c*) *The level of protein in the serum.* This has been considered by so many people with reference to oedema that it is unnecessary to do more than mention it. All that is known suggests that a fall in the serum proteins, particularly in the albumen fraction, will increase the rate of formation of tissue fluids. Furthermore,

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the evidence, which has already been discussed at some length, all points to the fact that the concentrations of both total protein and of albumen tend to fall in persons who are undernourished. The observation was made before the first world war and has been confirmed, reconfirmed, and discussed many times over, as a reference to the previous pages or to any of the following articles will show: Frisch *et al.* (1929); Bruckman and Peters (1930); Bruckman *et al.* (1930); Leiter (1931); Shelburne and Egloff (1931); Weech *et al.* (1933); Youmans *et al.* (1933); Peters (1935); Luckner (1938); Madden and Whipple (1940); Laroche *et al.* (1941); Govaerts and Lequime (1942); Gounelle, Bachet and Marche (1942b); Jiménez-Diaz *et al.* (1942); Leulier *et al.* (1942); Loeper *et al.* (1942a, b); Martin and Demole (1943); Brull (1945); Cardozo and Eggink (1946); Leyton (1946); van Oven (1946); Denz (1947); Bok (1949). In fact, the determination of serum proteins has become one of the recognized methods of assessing the state of a person's nutrition, and has been applied on a large scale in many parts of the world (de Venanzi, 1943–4). This, therefore, is one way in which undernutrition can and often must accelerate transudation from the vessels, and by so doing it might be expected to increase the sodium space in every part of the body.

(*d*) *Tissue tension.* Tissue tension is probably very important, but it has been relatively little discussed. Bönniger's (1905) early work on post-mortem material showed that the skin was always under tension *in situ*, and that it shortened after removal, more so if there was underlying oedema. Clinical observation would confirm this. Bönniger also found, however, that poor nutrition did not reduce the elastic properties of skin. This may be so, but the appearance and feel of the skin and subcutaneous tissues of a dehydrated or undernourished individual strongly suggest that these tissues are under subnormal tensions *in situ*. Attempts to measure tissue pressure by introducing hollow needles into the cutaneous and subcutaneous tissues have been made by Burch and Sodeman (1937), Holland and Meyer (1932), Meyer and Holland (1932), Wells *et al.* (1938), and others. The technical difficulties must be considerable and the findings are not easy to interpret. Meyer and Holland, for instance, recorded no increase in subcutaneous pressure after the venous pressure had been raised, but Burch and Sodeman and Wells *et al.* did so. Burch and Sodeman found increased subcutaneous pressures in people with oedema, but others have not, and no studies of undernourished people with or without oedema have been made. On the whole the pressures found have been surprisingly low, for they have usually ranged between 2 and 4 cm. of water, but, as several of the investigators have pointed out, the pressures must be low, lower always than the venous pressures, for if they were not the veins would collapse. Thomson, Thomson and Dailey (1928), Waterfield (1931a,b), and Looke (1935–7) measured the increase in the volume of the leg which took place on changing from the recumbent to the vertical position. They found that at first the leg increased in volume, and they brought forward good evidence that this was due to increased transudation from the blood vessels. However, after 30 to 50 minutes, or longer in some instances (Looke, 1935–7), the legs ceased to increase in volume, and Krogh *et al.* (1932) and Landis and Gibbon (1933) pointed out the part played by tissue elasticity in bringing this about. The gross increase in subcutaneous pressure—up to 25 cm. of water—which may follow experimental frostbite, and the part played by it in limiting further oedematous expansion in the volume of the limb, have been described by Fuhrman and Crismon (1947).

A good tissue pressure must help to promote lymphatic drainage, which Weech *et al.* (1934) showed in a dog to be free enough during movement to carry off the surplus interstitial fluid that collected in the legs during rest, even when the animal had very low serum proteins. Looke's (1935–7) experiments suggest that the same is true of healthy men and women in the erect attitude. Partial failure of the lymphatic drainage from a limb would certainly favour the accumulation of tissue fluid there, and if the skin and tissue pressures are low in wasted limbs this may be one of the reasons why fluid collects in them so easily (Lohr, 1947). The work of Weech *et al.* and of Looke also showed the importance of movement in promoting drainage. This has been shown by many other people, and reduced activity may well be a factor in the causation of hunger oedema, for if undernourished people are forced to stand or to walk their movements are likely to be less in both variety and amplitude than those of fit men (see Smirk, 1935–6b).

If tissue tension depends in any way upon the elastic fibres in the skin and subcutaneous tissues—and it surely must—an explanation is at once provided for one of the most characteristic clinical features of hunger oedema, namely the tendency for men over 40 to be the first sufferers in a mixed population. It is in this sex and at this age that elastic tissues tend to degenerate even in well-nourished persons. The aorta tends to widen and the skin to wrinkle and crease (Stieglitz, 1943). The natural elasticity of the tissues is beginning to fail.

The Volume of the Sodium Space

As long ago as 1860 Bischoff and Voit stated that if a dog was starved or given only bread to eat the loss of weight caused by the catabolism of its own protein and fat might be masked by a simultaneous retention of water. Only a few experiments were carried out, but in 1881 Voit requoted some of the results to show that the composition of the body was not fixed and invariable. His view was that the tissues of very young or undernourished animals contained more water than those of normal adults, and that this was not merely because of the small amount of fat in them. This theory was supported by a number of later investigators. Mendel and Rose (1911–12), for instance, showed it to be true of undernourished rabbits' muscles, and Lipschütz (1911, 1915) and Morgulis (1915) demonstrated it in various species of fish. The evidence was summarized by Morgulis (1923a and b). The conception that undernutrition increased the percentage of water in fat-free tissues was, however, opposed by other investigators of whom Terroine may be taken as the representative (Terroine, Brenckmann and Feuerbach, 1922–3; Terroine, Feuerbach and Brenckmann, 1924). These authors considered that the composition of the "real" body of a warm-blooded animal varied from species to species, but within one species was fixed and almost immutable, and that the only real variable in the body was the fat reserve. There was a great deal of evidence even in 1923–4 to show that Terroine's position was untenable, for single tissues such as the plasma had been shown clearly to lose protein in undernutrition, and to lose water in dehydration (Roger, 1907). The bones also had been shown to be decalcified (Dalyell and Chick, 1921), but Terroine's conclusions were based upon starvation experiments with and without water, and not upon the results of chronic undernutrition, and a belief in the constancy of the composition of cell protoplasm during starvation was the basis of Gamble, Ross and Tisdall's (1923) classical paper, which has stood the test of time remarkably well.

The difficulties were largely resolved by an appreciation of the differences between extracellular and intracellular body water (Peters, 1935). Bischoff and Voit's (1860) experiments were confirmed by Weech *et al.* (1933, 1935b), who showed that the retention of water was accompanied by a retention of sodium salts. It is now known that in chronic undernutrition there is a great increase in the percentage of the body occupied by extracellular fluid (Beattie, Herbert and Bell, 1948) and that the sodium space may actually become greater than it was during health (Cachera and Barbier, 1943; Henschel *et al.*, 1947; Keys *et al.*, 1946; Markoff, 1946; Denz, 1947; Heller and Dicker, 1947; Dicker, 1948a, b; *Widdowson and McCance*, p. 165). The objections to relating any of these changes to the subject's body weight at the time the measurements were made were ably discussed by Cachera and Barbier (1943) and both these authors and Perera (1946) came to the conclusion that it was best to refer all such changes to the person's "ideal" weight. However expressed, this increase of extracellular fluids during undernutrition is common to all mammals, at all ages (Kerpel-Fronius and Kovach, 1948), and probably to all vertebrates, and is quite independent of the appearance of oedema (Heller and Dicker, 1947). The changes during complete deprivation of food require further investigation, but there is no longer any doubt that in chronic undernutrition the nitrogen/sodium ratio of the body falls, so that Terroine's theoretical contention need no longer be considered.

This increase in the body's sodium space is probably one of the most fundamental changes brought about by undernutrition. It far transcends in magnitude and theoretical importance the localized collections of extracellular fluid which constitute clinical oedema (see Keys *et al.*, 1946; Weech *et al.*, 1933, and *Widdowson and McCance*, p. 165), and the reasons for it must now be carefully considered.

Reasons for the Increase in the Sodium Space

(*a*) *A fall in the serum proteins.* This has already been discussed in the section that described in general terms the fluid equilibrium between the capillaries and the tissues. Once the level of serum proteins has fallen it is easy to attribute the enlargement of the sodium space to this fact, but the serum proteins may not fall, as already stated, and the sodium space may certainly enlarge before they do. Gsell (1945) was incorrect when he wrote that "Hypoproteinämie ist ein *obligates Symptom* der Hungeroedemkrankheit". If, moreover, the fall in the concentration of serum albumen were an important cause of the vascular-tissue fluid imbalance in undernutrition, one would expect on theoretical grounds to find the plasma volumes low. Chang (1931–2) held that they were, but there is something a little unsatisfactory about his evidence, for he determined the blood volumes by a carbon monoxide method and obtained no changes in haematocrit in spite of large changes in total blood volume. Weech (1938–9) put forward the idea that one of the functions of the serum albumen was the maintenance of the normal plasma volume and that a fall in the concentration of the albumen, however it might have been brought about, led to a reduction in the volume of circulating plasma. Bansi (1946a) and Cardozo and Eggink (1946) considered that the blood volumes were slightly reduced in undernutrition and Rossiter (1946) also found them to be low and to rise with recovery, but more experience has not altogether substantiated this (Schneider, 1947). Beattie *et al.* (1948), who tried to differentiate two kinds of hunger oedema on the basis of serum protein concentrations and response to treat-

ment, found that the absolute plasma volumes were those to be expected had their subjects lost no weight, i.e. the plasma volumes were abnormally large for the subjects' actual weights. Mollison (1946) found the blood volumes of the Belsen internees to be of the order of 100 c.c./kg. of body weight, which is higher by about 30 c.c. than the figures for normal people given by Gibson and Evans (1937a). Cachera and Barbier (1943) found the plasma volume in their cases of oedema to average 7·1 per cent of the ideal weight, 40 per cent higher than the normal, which should be about 5 per cent.

Indeed, the evidence is that the plasma volumes tend to increase or decrease as the volume of extracellular fluid rises or falls. Thus Henschel *et al.* (1947) showed that the plasma volumes of their experimental subjects rose from an absolute value of 3·13 l. to one of 3·41 l. after 24 weeks of restricted diet, and fell again after 11 weeks on the recovery diet. These changes would have been much greater if the volumes had been expressed as a percentage of the body weight. Brull and Op de Beeck (1944a,b) found that chronic undernutrition raised the volume of plasma per kg. of body weight in their experimental dogs, and finally Denz (1947) claimed that a few days' rest in bed caused the oedema of his patients to disappear with a considerable loss of body weight and a fall in the plasma volume (but see *Widdowson and McCance*, p. 165). In other words, the plasma is only one of the tissues participating in the general anasarca.

In spite, therefore, of the excellent work on animals and man which has pointed to a correlation between a fall in the concentration of serum albumen and the formation of oedema, the only conclusion possible at the present time is that a low level of serum albumen, or of total proteins, is not the deciding factor in the overproduction of tissue fluid in human undernutrition. More fundamental work is required on the effect of lowering the level of serum proteins on the plasma volume of animals. Some evidence has been produced by very sound investigators that the volumes will be found to fall (Bloomfield, 1933; Lepore, 1932–3; Weech, Wollstein and Goettsch, 1937). This aspect of the subject, including the possibility of species differences, has been reviewed by de Venanzi (1943–4).

(*b*) *Replacement.* The limbs of a healthy man consist of bones, well-developed muscles, some connective tissue and fatty deposits, and a covering of well-fitting skin and subcutaneous tissue. "There are no empty spaces containing free fluid in any normal tissue. The intercellular spaces are filled with a gelatinous protein matrix, and it is the fluid phase of this colloidal matrix which constitutes the tissue fluid" (Trowell, 1946). The shape of the limb depends upon the size of the underlying structures and the elastic properties of the skin. In a wasted person the muscles may be only half their normal size, there will have been a loss of protein from the gelatinous intercellular matrix, and the fat deposits may have gone. It has been suggested very reasonably that their place will be taken to some extent by extracellular water (Jiménez-Diaz *et al.*, 1942; Trowell, 1946), and there is positive evidence that the replacement of pre-existing bodily structures with extracellular fluid is one of the most important reasons for its accumulation in undernutrition. The fatty bone marrow, for instance, was long ago observed to become a watery mass of fibrils and cells during starvation (Roger and Josué 1900a, b), and if fat or muscle atrophies inside a rigid framework, replacement with a watery phase is inevitable. This no doubt explains why lobsters lose practically no weight on starvation (Morgulis, 1916). Bettinger (1921), Mathias (1919b), Prym (1919–20; 1921), and Lubarsch (1921b)

all noted the replacement of fat in the normal depot sites with a mass of aqueous gelatinous tissue. Uehlinger (1947) made a great point of this, and Dicker (1948b) considered that the water administered by mouth to his hypoproteinaemic rats collected in these sites, and he commented upon the distended appearance of the gelatinous peri-renal and deep mediastinal connective tissues. So far as the limbs are concerned, the natural elasticity of the skin and subcutaneous tissues sets a limit at first to the replacement process, but as the limbs decrease in size the elastic properties of the skin are seldom good enough to prevent its becoming wrinkled and loose, and there is then little to stop the subcutaneous tissues becoming infiltrated with extracellular fluid. This loose wrinkled skin may closely resemble that of a person who is dehydrated, and it is this superficial similarity which has no doubt given rise to the belief that people can be both oedematous and dehydrated at the same time (Burger *et al.*, 1945).

(*c*) *Ratio of body surface to body weight.* The skin and subcutaneous tissues are important sodium depots and hold a considerable percentage of the extracellular fluid in the body. It is likely that the absolute amounts of sodium held per unit area of the skin and subcutaneous tissues will be increased in undernutrition owing to fat replacement there (Uehlinger, see Hottinger *et al.*, 1948), and it is certain that as the body wastes the area and volume of the skin and subcutaneous tissues will fall less than the body weight. Hence these changes will tend to increase the percentage of the body weight occupied by extracellular fluid (Kerpel-Fronius and Kovach, 1948).

(*d*) *The suprarenal cortex.* Most organs of the body lose a considerable amount of weight during undernutrition, and although this appears also to be true of the suprarenal cortex in young children (Nicolaeff, 1923), the cortical parts of the suprarenals of older children and adults have usually been reported to be of normal size (Gounelle, Marche, Bachet and Digo, 1942) or even hypertrophied with signs of adenomatous enlargement (Simonart, 1945). The cortical cells have frequently been reported to have lost their lipoids and lipoid pigments (Mathias, 1919a; Bettinger, 1921), but Prym (1919–20) found those in the outer zone to contain much pigment. The histology has been brought up to date and generally confirmed by Uehlinger (see Hottinger *et al.*, 1948), who emphasized the extensive loss of fat and the watery vacuolated swelling of the cells. He noted also some fibrosis of the capsule and zona glomerulosa. Liver cells of the dog have been shown to swell in a somewhat similar way after a prolonged deficiency of Calories and protein (Elman and Heifetz, 1941).

Sinclair (1948) has suggested that the hypertrophy of the suprarenal cortex, as evidenced by post-mortem weights, is responsible for the retention of sodium and water. He has postulated, in other words, that there is too much of the desoxycorticosterone type of hormone in the body. There is, moreover, some quite independent evidence, which has been summarized by White (1948), that the suprarenal cortex may be in a state of functional activity during inanition. One of the most important functions of the adrenal cortical hormones is to mobilize tissue proteins if and when they are required for gluconeogenesis, and many experiments and observations, starting with those of Addison, have shown that there is an inverse relationship between the activity of the cortical hormones and the state of development of the lymphoid tissue. This tissue rapidly atrophies in the mouse during the first two days of starvation, but only if the suprarenal glands are present and functionally active. Nicolaeff (1923) made a special point of the extreme atrophy of the thymus in children who had died of undernutrition, and Oberndorfer (1918) emphasized the great reduction

of all the lymphoid tissue in the spleen. Both these observations suggest activity, but not necessarily overactivity, of the cortical hormones in human undernutrition. Uehlinger (see Hottinger *et al.*, 1948) and others, moreover, have not regarded the histological evidence as indicating an overproduction of hormones, and it is well known that anatomical enlargement may not indicate functional hypertrophy. The thyroid enlargement in goitre areas is a case in point. Arocha and de Venanzi (1943–4) and de Venanzi, Soto-Rivera, Galíndez and Poleo (1943–4) showed that intravenous injections of cortical hormones into healthy dogs and man produced a rise in the serum proteins, but their change was rapid and transient and the observations probably do not affect the present issue except in a general way.

Deane, Shaw and Greep (1948) showed that sodium deficiency in rats produced hypertrophy of the zona glomerulosa, or outer parts of the cortex, and a reduction and ultimately a disappearance of lipoid from the cells of this area. Unfortunately, this stimulating contribution to knowledge does not help to interpret the post-mortem evidence. If the experimental findings are taken to indicate the appearances brought about by overproduction of the desoxycorticosterone type of hormone, then the post-mortem evidence of hypertrophy, vacuolation, and loss of pigment might be taken to suggest that the human tissue had been subject to the same influences, but there are several considerations to set against hypertrophy of the suprarenal cortex in human undernutrition. The first is the abundance of pigment sometimes found in the outer cortex (Prym, 1919–20; Nicolaeff, 1923; Schulten, 1946). The second is that Uehlinger noted fibrosis there. The third is that since undernourished people may die of hypoglycaemia (Gounelle, Marche and Bachet, 1942b; Gounelle, Marche, Bachet and Digo, 1942; Lhermitte and Sigwald, 1942; Bellier, 1943; Levrat and Roche, 1943; Levrat *et al.*, 1943; Levrat, 1944) it is unlikely that there is ever an excess of the sterol catalysing the conversion of protein to carbohydrate in the circulation during the later stages of undernutrition, unless it is the liver which fails to make the conversion. The fourth consideration is that many people during the first and second world war have commented on the lymphocytosis and mononucleosis found in the peripheral blood during undernutrition (Knack and Neumann, 1917; Maase and Zondek, 1917b; Lewy, 1919; Sehrt, 1921; Girard *et al.*, 1942; Leulier *et al.*, 1942; Bansi, 1946a; Schäfer, 1946). These findings do not suggest atrophy of the lymphoid tissue, and Uehlinger (see Hottinger *et al.*, 1948) particularly noted that the lymphoid follicles in the spleen were not atrophied in people who had certainly died in the last stages of undernutrition. Fifthly, the pigmentation (Bok, 1949) and the low blood pressures, so characteristic of undernutrition, suggest atrophy rather than hypertrophy of the cortex. Subnormal adrenaline production has been reported (Peiser, 1921), but the evidence was very slender. Lastly, there is a good deal of evidence, which has been summarized and reviewed by Chambers and Zweifach (1947), that the hormones of the cortex decrease the permeability of the capillaries. They have actually been shown experimentally to reduce the formation of oedema fluids. If a hormone acts on different organs in an antagonistic way, it is the net effect which counts, but this may be very difficult to predict in all circumstances, and this "anti-oedema" effect must not be forgotten if a large sodium space or the formation of oedema is being attributed to cortical hypertrophy.

It is quite clear that on this subject interesting suggestions have been made to explain the increased volume of extracellular fluid found in undernutrition (Simonart, 1945; Sinclair, 1948), and the way is now open for a great deal of

work both in the laboratory and the field. No doubt it will be done, but for the moment no more can be said.

(*e*) *The intake of salt.* There is at least one other reason why undernutrition, as it has been seen in epidemic form in central Europe, should lead to an increase in the body's sodium space. It is the practice of people who are undernourished and hungry to take a great part of their sustenance in the form of soups which are generally made with plenty of salt since other seasonings are frequently unobtainable. The intakes of salt are often very high, and there is no doubt that the volume of extracellular fluids can be raised and maintained at a high level in this way (Veil, 1914, 1923; Lyons, Jacobson and Avery, 1944; Lyons, Jacobson and Neerkin, 1945; Leaf and Couter, 1949; Leaf, Couter and Newburgh, 1949). Jansen (1920) showed that the administration of 34 g. of salt per day to a cachetic woman with carcinoma of the oesophagus increased her weight by more than 6 kg. and that it fell again when the intake of salt was reduced to 2 g. Weech *et al.* (1933) demonstrated a similar relationship, and many other people have done the same both in animals and in man (Hume, 1911; Hülse, 1919; Weech and Ling, 1931; Liu, Chu, Li and Fan, 1932; Loeb *et al.*, 1932; Laroche *et al.*, 1941). The converse of this is also true. Reducing the salt intake of a normal person to a very low level is followed by a rapid fall in the body weight till equilibrium is re-established (Leaf and Couter, 1949; Leaf *et al.*, 1949). McCance (1935–6), for example, lost 1·5 kg. in less than two days on a "salt-free" diet before he began to make himself really salt deficient by sweating. Reducing the salt intake has commonly been employed by clinicians in the treatment of hunger oedema (Gounelle, Bachet and Marche, 1943; Justin-Besançon, 1946), but the effects have generally been masked by other treatments. A high intake of salt is not, however, one of the essential requisites for an abnormally large sodium space nor need it always operate whenever the intake of food is sufficiently reduced. The absence of any salt in the ingesta, for instance, may explain why complete starvation never gives rise to a visible accumulation of extracellular fluid, and the fact that patients with anorexia nervosa eat so little and often vomit so frequently—in fact voluntarily—is certainly one of the reasons why they do not get visible oedema; their age and sex are others (*vide supra*).

(*f*) *Posture and exercise.* These are such important causes of clinical oedema in an undernourished community that any influence that they can possibly have on the size of the sodium space must be carefully considered. Within recent years the kidney has become implicated in cardiac oedema, and it is now accepted that this organ must retain sodium and chloride in heart failure because in cardiac, as in hunger, oedema, the plasma volume is higher, not lower, than normal. Theoretically it should be lower only if the oedema is due to back pressure (Gibson and Evans, 1937b; Seymour, Pritchard, Longley and Hayman, 1942; Annotation, 1948b). Both the erect attitude (Brun, Knudsen and Raaschou, 1945a,b; *McCance*, p. 175) and exercise (van Slyke, Alving and Rose, 1932; White and Rolf, 1948) may greatly reduce the glomerular filtration rate, and some recent work on cardiac oedema (Merrill, 1946; Mokotoff, Ross and Leiter, 1948) has been held to show that a fall in the glomerular filtration rate, sometimes accentuated by exercise (Merrill and Cargill, 1948), is the cause of this kind of oedema. It was supposed that the reabsorption of sodium was so closely coupled with the glomerular filtration rate and the reabsorption of water (Pitts and Lotspeich, 1946; Lotspeich, Swan and Pitts, 1947) that when the rate fell the amount of sodium available for excretion became smaller than the amount the body should excrete. It has now been shown, however, that the

glomerular filtration rate is not necessarily low in heart failure with oedema and decompensation (Briggs, Fowell, Hamilton, Remington, Wheeler and Winslow, 1948; Farnsworth and Krakusin, 1948), nor need it improve as the excretion of sodium rises with recovery and recompensation. Thus, although the reabsorption of much sodium chloride must be linked with the reabsorption of water (Lotspeich *et al.*, 1947)—and therefore with the glomerular filtration rate—there would appear always, except possibly during a salt deficiency, to be a sufficient excess left after the obligatory reabsorption is finished to be taken up *or not* by the distal tubule according to the needs of the body. Too much sodium chloride is reabsorbed certainly in heart failure with decompensation, and possibly in undernutrition also, but the reason is unknown. There is, indeed, no convincing evidence that the glomerular filtration rates are appreciably subnormal in undernutrition, or that they are reduced to a greater extent by the erect attitude or by exercise in undernourished than in normal persons (*McCance*, p. 175). If they were, the effects should be demonstrable clinically, as they so often are in cardiac failure, by a study of the urea clearances and blood ureas.

Govaerts and Lequime (1942) supposed that the inhibitory effect of the erect attitude upon the excretion of water was a reason for the retention of water in undernutrition, but again there is no evidence at present that the excretion of water is more reduced by the erect attitude in undernourished than in normal persons (*McCance*, p. 175). There is, therefore, no proof that the erect attitude or exercise enlarges the sodium space in undernutrition, any more than it does in health, by a "central" action on the kidney.

(*g*) *Unbalanced production of antidiuretic hormones.* Work which was being done on the function of the liver and on diets thought to be injurious to this organ suggested that unbalanced production of antidiuretic hormones might be responsible for the increase in the sodium space. Leslie and Ralli (1947) showed that rats fed on a low-protein high-fat diet continually produced a large excess of some antidiuretic material, so that their response to a test dose of water was slower and much less complete than the normal one. Ralli, Robson, Clarke and Hoagland (1945) had already claimed that patients with cirrhosis and ascites excreted something in their urine which acted as an antidiuretic when injected into rats. The ability of a low-protein diet to reduce the diuretic response of rats to a test dose of water has been amply confirmed by the workers at Bristol (Dicker, 1948b, 1949) who imply that some such cause must be operating in human hunger oedema. Unfortunately the experiments carried out in Germany did not support this (*McCance*, p. 175), for the response of undernourished and oedematous persons to test doses of water was not found to differ significantly from the normal. If, furthermore, an abnormal liver is a prerequisite for the production of this non-dialysable antidiuretic hormone, there is no reason to believe that an excess of it would have been produced by undernourished people in Germany, for the livers of such people were found to be normal (*Sherlock and Walshe*, p. 111).

(*h*) *A deficiency of aneurin.* Patients suffering from beriberi often develop oedema, and when this disease was found to be due to a deficiency of aneurin it was natural to associate a vitamin deficiency with the aetiology of any nutritional oedema. The problem came up during the first world war and was discussed by Rumpel and Knack (1916), Hülse (1917), and Schittenhelm and Schlecht (1919c), all of whom decided on clinical grounds that the oedema under observation at that time was not due to a deficiency of vitamin B. Nor were

the oedemas produced in rats by Frisch *et al.* (1929) and Luckner (1938) shown to originate in this deficiency. The matter was raised again during the recent war (Sivadon, 1941; Simonart, 1941, 1942, 1945; Devis and Simonart, 1942). The evidence of most authors has been against the association (Crismer, 1941a, b; Durand, 1942; Bruun, 1947), but Simonart, and also Heilmeyer (1946) strongly supported it. Devis and Simonart (1942) and Heilmeyer (1946) considered that the blood pyruvates were raised, but this estimation requires careful interpretation (Taylor, Weiss and Wilkins, 1937). Simonart worked mostly with prisoners in the gaol at Louvain, and he based his claim for the importance of aneurin mostly on the effects of treatment. In the main this was well controlled in that the administration of the vitamin was the only variation made in the life of the prisoners, but for long periods 20–100 mg. were given daily, quantities which far exceed those required to correct any possible deficiencies, and have been said to be toxic (Leitner, 1943). Simonart also emphasized the curious point that the vitamin had often to be given intravenously to cure the oedema. Gains in weight, often spectacular, were produced by intramuscular injections of similar amounts for periods of up to 40 days. Simonart's book contains many very sound and interesting observations on undernutrition, but the effects of aneurin require further investigation, and if posible experimental verification in animals.

Heilmeyer (1946) considered that the nutritional oedemas in Germany were sometimes due to a deficiency of Calories and protein, and hence to low serum proteins, sometimes to a deficiency of aneurin, and sometimes to both. The patients with vitamin deficiencies were said to have large flabby hearts and the oedema was attributed to a form of heart failure. It is difficult to see how these patients can have been short of aneurin, but anyone acquainted with the difficulty of making a firm diagnosis of uncomplicated hunger oedema in an elderly man will appreciate that Heilmeyer has taken up an almost impregnable position, because at an advanced age heart failure can always be invoked as well. Firm proof of the vitamin deficiency, however, is necessary to establish the diagnosis. Reports of cures after the administration of enormous doses of aneurin to patients are unconvincing because of the ease with which nutritional oedema comes and goes, and each case must be considered on its merits (Merklen, Gallot and Gouygou-Roth, 1942).

(*i*) *Thyroid deficiency*. The effects of starvation and undernutrition on the oxygen consumption had been investigated experimentally (Mühlmann, 1899; Benedict, 1907; and others, see Grafe, 1928) before the war of 1914–18. Morgulis, Diakow and Zuntz (1913) showed that in chronic undernutrition the resting metabolic rate of a dog fell from 931 to 631 Cal. per sq. m. per 24 hr. Loewy and Zuntz demonstrated the effect on themselves in 1916 and made a further report on their basal metabolic rates two years later (Zuntz and Loewy, 1918; see also Benedict *et al.*, 1919). The number of cases of thyrotoxicosis at one of the Hamburg clinics fell from 217 during the five years preceding the war to 42 between 1915 and 1920 (Curschmann, 1923). These results have been confirmed during and since the recent war by Brull (1942), Govaerts and Lequime (1943), Heilmeyer (1946), Bansi (1946b), Frey (1947), and Henschel *et al.* (1947). The basal metabolic rate has been shown to be unexpectedly low both in people who were previously normal and also those who had thyrotoxicosis, and not to rise, moreover, to the expected height if undernourished people developed this disease. Jansen (1920) commented on the extreme atrophy of the thyroid glands in the bodies of undernourished persons. Flesch (1917)

claimed that thyroid medication helped to remove the oedema, but this was disputed by Schiff (1917b) at the same meeting. Schittenhelm and Schlecht (1919b) believed that the administration of thyroid greatly increased the elimination of water in undernourished but not in normal persons, but no one has claimed to have found any correlation between the fall in the basal metabolic rate and the extent of the oedema. Whatever may be true of undernutrition, moreover, it was shown by Beaumont and Robertson (1943) that patients with myxoedema had normal powers of concentrating their urines and of excreting water under test. Duvoir *et al.* (1942) reopened this question by reporting on a man aged 43 who had lost half his original weight and had a basal metabolic rate of −27 per cent of normal. The patient did not get rid of his oedema with rest and a salt-free diet, but on receiving thyroid he began to excrete large volumes of urine and to lose his oedema. A single case counts for little in a problem of this kind and the authors would have done well to have searched for other cases of a similar kind or to have made some experiments on animals. There has been much loose writing within the last ten years about the effects of general endocrine deficiencies in undernutrition (Loeper *et al.*, 1942a; Mauriac *et al.*, 1942; Strauzenberg, 1946), but the opinions put forward will have little appeal to those who are approaching the subject in an experimental way.

(*j*) *Diarrhoea.* The association between diarrhoea and hunger oedema is an interesting one. Rumpel (1915) and Rumpel and Knack (1916) originally suggested that the diarrhoea caused the oedema, and this idea has been revived by Herrlich (1947) and Markoff (1946). This at first sight may seem surprising, for the *curative* effects of diarrhoea on oedema and ascites were observed much earlier and are better established. They formed the basis of two of the aphorisms (Hippocrates, *c.* 450 B.C.)—ἢν ὑπὸ λευκοῦ φλέγματος ἐχομένῳ διάρροια ἐπιγένηται ἰσχυρὴ, λύει την νοῦσον—and the therapeutic possibilities of inducing diarrhoea were fully appreciated by Celsus (*c.* 0) and Galen (*c.* 160). "Si per talia auxilia venter non siccatur, sed humor nihilominus abundat, celeriori via succerrere, ut is per ventrem ipsum emittatur" (Celsus, *c.* 0). Many similar observations have been made in more recent times. The dehydrating effects of cholera, for instance, are well known, and diarrhoea may be said to have cured the first and fourth cases of oedema described by Wagner (1887). All the work, moreover, which has been carried out since 1925 has made it clear that diarrhoea must reduce the body's sodium space and so prevent or reduce any accumulations of extracellular fluid (Turner, 1932; McCance, 1936; Mach, 1946; Gamble, 1947). The absence of oedema in so many of the emaciated people found at Belsen (Mollison, 1946) may have been due to the fact that they had had so much diarrhoea (Lipscomb, 1946).

There is, nevertheless, an association between diarrhoea and hunger oedema in that both are the products of prolonged undernutrition (Bok, 1949). Before the 1914–18 war the enteric group of diseases may have dominated the picture, but diarrhoea has accompanied every famine in history. It played its usual role in Finland, for instance, in 1868 (Sievers, 1930) and it was a great feature of the Irish famine (McCormick, 1847). "The surgeon of the dispensary there [Westport] describing the people as swept off by dysentery, the most usual form of the famine plague, by ten to twenty a day" (Forster, 1847). Donovan's (1848) autopsies showed that this "dysentery" was often associated with considerable ulceration of the lower bowel, but there is no reason to suppose that this was due to specific pathological infections. Park (1918), for instance,

reported that none could be found and also that well-fed people exposed to the same conditions and chances of infection did not get diarrhoea. In the recent war also it has been common to find no pathogenic organisms in the stools in spite of recurrent or, in the later stages, of intractable diarrhoea. There probably were none, and the changes found in the gut after death (Donovan, 1848; Lubarsch, 1921b; Simonart, 1945; Uehlinger, 1947; Thaysen and Thaysen, 1949) are quite enough to explain its intolerance to food in the later stages of undernutrition and the passage of much undigested matter (Laycock, 1944). Apart from all this, chronic diarrhoea must lead to a great loss of nitrogen in the stools and, according to Bansi (1946b), undernourished people can lose up to 4 g. of nitrogen per day in this way, even in the absence of frank diarrhoea. This seems excessive, and there are other rather unexpected findings in the same paper, but a colitis and more particularly an ulcerative colitis can deplete the body of a great deal of protein (Welch, Adams and Wakefield, 1937; Annotation, 1937). The serum proteins may be so reduced by this (Moschowitz, 1933; Binger and Keith, 1937; Johansen, 1938) that oedema becomes almost inevitable if and when the stools become less numerous (Simonart, 1945; Anon., 1948). Holten (1941) commented on the fact that his subject did not have oedema although the serum proteins had been reduced by colitis.

Pathological changes of this type, or some similar sequence of events, probably underlie the clinical findings of many people, e.g. Hume (1911), Laroche *et al.* (1941), Liu, Chu, Wang and Chung (1932), and Simonart (1945), who have repeatedly emphasized the onset of oedema in association with little bouts of diarrhoea. Thus, although diarrhoea might be expected as a rule to remove oedema by forcing the excretion of sodium salts and water, given the appropriate conditions it may lead to oedema by decreasing the general level of nutrition and more directly by helping to lower the serum proteins.

(*k*) *Heat and cold.* Many authors from Chiari (1916) onwards have suggested that cold or exposure may have helped to bring on the oedema (Lange, 1917; Schittenhelm and Schlecht, 1918; von Hoesslin, 1919; Guillermin and Guyot, 1919; Simonart, 1945; Heilmann, 1946). Knack and Neumann (1917) suggested that cold might operate by raising a person's Calorie requirements and so increasing his undernutrition, and also by causing local damage to the capillaries. Both these suggestions require serious consideration in assessing the causes of the oedema in the Antarctic explorers or in Napoleon's troops during the retreat from Moscow in 1812 (*vide supra*). Lewis (1939–42) showed by experiment that exposure of a limb to cold made it oedematous and the work on immersion foot which was carried out during the recent war demonstrated how easily oedema could be produced by cold and wet (Ungley and Blackwood, 1942; Editorial, 1943; Medical Research Council, 1943; Goldstone and Corbett, 1944).

On the other hand oedema is well known to be made worse by warm weather (Simonart, 1945), and people who have never had oedema may develop it during a voyage through the Red Sea (Castellani, 1930–1). Drury and Jones (1927) demonstrated that warmth increased the passage of fluid from the capillaries and Turner *et al.* (1930) showed that the swelling on the legs of young women in the first 15 minutes after they stood up was greater in summer than in winter. Some of this swelling, however, was caused by blood collecting in the dependent vessels, and the number of subjects examined in the summer was rather limited. The experiments of Drury and Jones (1927) were better ones, and there can be no doubt about the clinical association of oedema with warmth. Courtice

(1946) showed that cooling a scalded limb decreased the exudation of fluid into it, and this principle became the basis of the treatment of immersion foot (Ungley, 1943). In this connexion it is worthy of record that Cohnheim clearly pointed out in 1889 that "the endothelium of the vessels is an organ with an active metabolism [see also Chambers and Zweifach, 1947] and for it to remain normal the blood bathing it must not depart to any considerable extent from the normal standard, either in composition, amount, velocity, or temperature". If unfavourable temperatures promote oedema in normal persons they would certainly accentuate the tendency of undernourished people to develop it. Their action, however, particularly that of cold, would generally be localized and might produce oedema of the ankles without measurably or actually increasing the body's sodium space. Extremes of temperature should certainly be considered in assessing the cause of peripheral oedema in undernourished persons who have been exposed to them, but they should never be regarded as having any primary action, as undernutrition has, on the body's sodium space.

Reconsideration of Some of the Clinical Characteristics

Although the reasons may still be obscure, particularly in individual cases, there is now good evidence that undernutrition leads to an increase of the body's sodium space. In the main this space is filled with a fluid which is neither intracellular nor intravascular and which is consequently "free" to move under the influence of gravity. This fluid will inevitably tend to collect in the dependent parts of the body and lack of the normal elasticity of the tissues will facilitate the process. The undernourished person must be regarded as carrying far too much extracellular fluid for his needs inside a skin which is too large for the volume of the tissues enclosed by it. Looked at in this way the problem becomes one of discovering not so much why some undernourished people get oedema as why all undernourished people do not. It is helpful here to refer back to some of the clinical characteristics of nutritional oedema.

It has been realized for a long time that many of these characteristics are really the effects of posture (Govaerts and Lequime, 1942; Maase and Zondek, 1917b). Changing from the erect to the recumbent attitude has been known since the last century to increase the urine flow of a normal man. The matter was first investigated out of interest in orthostatic albuminuria but has repeatedly been confirmed for other reasons (Edel, 1901; Linossier and Lemoine, 1903; Erlanger and Hooker, 1904; Seyderhelm and Goldberg, 1926; White, Rosen, Fischer and Wood, 1926; Ni and Rehberg, 1931; Asmussen, Christensen and Nielsen, 1938; McCann and Romansky, 1940a, b; Brun *et al.*, 1945a, b; Theobald, 1946). Some of the work has indicated that an increase in venous pressure in the kidney on the assumption of the erect attitude is the cause of the albuminuria (Bull, 1948), but the fall in urine volume which takes place at the same time is not confined to adolescents with orthostatic albuminuria, and has a much wider interest. Asmussen *et al.* (1938) showed that the fall could be prevented by bandaging the legs, but did not consider that it was simply a matter of fluid collecting in the legs and so failing to be excreted.

Ni and Rehberg, McCann and Romansky, Brun, and others have analysed the role of the kidney. All came to the conclusion that there might be a considerable fall in the glomerular filtration rate of a subject on assuming the erect attitude and standing very still, but that increased reabsorption by the tubules was often a more important reason for the fall in urine volume. It has been shown that the fall in the output of water is generally accompanied by a fall,

but a smaller one, in the output of sodium chloride, and Seyderhelm and Goldberg (1926) found that after drinking normal saline the diuresis was not so large as it was after an equivalent quantity of water, but that the effects of a change of posture were otherwise similar. It is evident that a change of posture brings about a group of complicated and to some extent interlocking effects, but a study of the changes in the glomerular filtration rate (*vide supra*), in the response to a water diuresis (*McCance*, p. 175), and in the concentrations of serum proteins (Gounelle, Bachet and Sassier, 1943; *Widdowson and McCance*, p. 165) has not revealed the differences that might have been expected between normal and undernourished persons.

There are, however, gross differences in urine flow under the appropriate conditions. The normal man, for instance, is not usually afflicted by nocturnal polyuria, which is one of the worst troubles of the undernourished, even if they do not fill themselves up with soup at their evening meal. Nocturnal polyuria, however, is, or may be, one of the trials of pregnancy, and Theobald's (1946) paper on the subject is most stimulating to anyone interested in its aetiology in undernutrition. Pregnant women, it seems, do not get a normal diuresis after taking water by mouth if they are standing or sitting, and they readily develop oedema of the legs when they are up and moving about (Looke, 1935–7). There are still many things about the fluid metabolism of pregnancy which are not fully understood, the large plasma volume, for instance (Thomson, Hirsheimer, Gibson and Evans, 1938), but it is natural to attribute this oedema of the legs to increased venous pressure caused in them by the enlarged uterus resting on the iliac veins. On lying down the excess of extracellular fluid in the legs is reabsorbed into the veins owing to the fall in venous pressure and the re-establishment of a free flow of blood, and the fluid is then excreted by the kidney. Undernourished individuals who are not handicapped by mechanical obstacles to the venous return from the lower limbs such as pregnancy imposes, nevertheless have a large excess of "free" extracellular fluid inside them, much of which by evening may have gravitated into the legs and taken up a position outside the general circulation. When they lie down this fluid in the legs becomes available for reabsorption into the blood vessels and hence for excretion by the kidney. The urine passed by undernourished people on lying down contains about 1 per cent of sodium chloride and should be regarded essentially as being derived from extracellular fluid.

It is the change of posture that makes a rest in bed so helpful to the recovery from hunger oedema, and the mechanism of its action is exactly the same as that by which it produces the nocturnal polyuria. Exercise is always taken in the erect posture and the ease with which it produces oedema in an undernourished person is in all probability due to this. It is difficult to believe that exercise in a recumbent position would bring on pitting oedema in a person who did not have it already, and one would expect muscular movements in a recumbent attitude to favour the return of tissue fluids to the vessels through the lymph channels (Theobald, 1946), but the effects of exercise in promoting the outflow of tissue fluid in normal and undernourished persons have never been compared (Drury and Jones, 1927).

The tendency of hunger oedema to recur and to persist can easily be explained. So long as a person remains undernourished all the forces which originally brought on the oedema remain in operation. A few days rest or a diet containing less salt may temporarily reduce the sodium space and dispel the visible oedema, but the stage is set for its return the moment the predisposing conditions are

restored. There is, however, another reason. Once a persons's tissues have been stretched by a collection of oedema fluid, they will naturally stretch more easily a second time. The elastic and fibrous tissues, which hold the muscle bundles together and impart that exquisite flexibility to the skin, and the gelatinous colloidal matrix between the cells may take months to regenerate and recover their properties, and this process will be much slower in elderly people than in those in the prime of life. It is uncertain to what extent, if at all, elastic tissue regenerates in men over fifty or sixty years of age.

Past, Present, and Future

The object of a review such as this is to make use of knowledge which has been acquired in the past in order to solve the problems of the present. In attempting to do this, it always becomes obvious that there are many gaps in our knowledge. These may be small or large, but to fill them is a task for the future.

The outstanding question about fluid metabolism today seems to be this: What regulates the volume of the plasma and of the extracellular fluids in health? The regulation of the composition of body fluids is much better understood, and methods for its study are available, but the volume of the extracellular fluids is not very closely maintained, even in health, and there are no exact methods of following the whys and wherefores of its fluctuations. Until these problems are solved, no full explanation of the changes in undernutrition is likely to be forthcoming.

While interest centred on the causation of visible oedema, progress towards the discovery of its aetiology was inevitably slow because laboratory animals do not readily become oedematous, but now that an increase in extracellular fluids has become established as an integral feature of undernutrition, the extension of our fundamental knowledge of the pathology underlying the expansion of the sodium space is likely to be more rapid, and may throw light on the normal mechanisms of regulation.

There remains the problem of the aetiology of the oedema. It seems very improbable that this will ever be solved by more descriptions of clinical material. This period of progress is past. Posture, however, is such an important element in the production and removal of hunger oedema that clearly there must be some demonstrable differences between the normal and the undernourished in their response to gravity. There is still naturally much to be learned about the normal responses, but they have been studied with some care and the subject was reviewed by Hellebrandt and Franseen in 1943. The departures from the normal in the undernourished are, however, not yet known, although various suggestions have been made, and the attempts to discover them have not so far been very searching, nor very successful. When it is next possible to study persons suffering from undernutrition side by side with normal persons of the same age and sex, controlled comparisons of some of the effects of posture should reveal differences in the cardiovascular-tissue equilibria which will explain the appearance of oedema in one, but not in the other.

SUMMARY

1. References to and good descriptions of hunger oedema can be found in books and papers written in the last century, in the Middle Ages, and in much earlier times, but they are few and far between, particularly when one considers the great wealth of information available about famines at all periods of history.

It is suggested that this paucity of information about what has become a very characteristic feature of undernutrition is due to the fact that the metabolic effects of a shortage of food were masked by the great epidemic diseases that always accompanied famine and undernutrition till well into the present century.

2. During and after the first world war a large literature, which was mostly the work of German authors, appeared on the subject of hunger oedema. By 1923 this aspect of undernutrition had been very fully described, so much so that its importance had become very much overemphasized.

3. It now seems clear than an increase in the percentage of the body occupied by extracellular fluid is the essential departure from the normal organization of the body water in undernutrition. Visible oedema is only one aspect of this, and many people never exhibit it. It is rare in animals and only common in man because he assumes the erect attitude.

4. Many theories have been advanced to explain the changes in fluid metabolism brought about by undernutrition. None are entirely satisfactory in that no one of them will explain all the facts, and it is probable that there are several causes both for the increase of extracellular fluid and for the appearance of pitting oedema.

5. It is suggested that the replacement of body space previously occupied by fat and cellular tissue is an important cause of the increase in extracellular fluid. If and when there is a fall in the concentration of serum proteins it is natural to suppose that this will also operate, and a large intake of salt must also help. Theories based upon overactivity of the hormones of the suprarenal cortex, a deficiency of aneurin, underactivity of the thyroid, extremes of heat and cold, and abnormalities of renal function must be regarded for the moment as not proven.

6. The appearance and disappearance of visible oedema in man is undoubtedly connected with posture, and the presence in the body of so much extracellular fluid free to move under the influence of gravity. It is not yet clear if any local abnormality need be invoked to explain the oedema, but it is natural to suppose that a reduction of muscle size and intercellular colloid, and a loss of elastic fibres from a skin now too large for the structures it was designed to enclose, will all favour localized collections of fluid in the dependent parts.

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III. THE EFFECT OF UNDERNUTRITION ON THE SKIN

by R. A. McCance and A. M. Barrett

PREVIOUS OBSERVATIONS

The skin is an organ which all can see, and it is no new observation that its appearance changes in times of famine and undernutrition. "Our skin was black . . because of the terrible famine" (Lamentations, v, 10) may well be one of the earliest allusions to pigmented "hyperkeratosis" or possibly to scurvy. It is unlikely, however, that blackening of the skin was ever a common manifestation of undernutrition, and most later writers on this subject have been struck by an altogether different appearance. "Mirabile dictu, nulli in terra nostra manserat naturalis color, sed talis pallor affinis et proprius mortis inerat universis" (Galbertus, 1125). This undoubtedly refers to the curious pallor which has defied description in more languages than one, but which observers ancient and modern have so frequently associated with undernutrition—whether complicated or not by malaria, anaemia or dysentery (Rodulfus Glaber, 1046; Hecker, 1844; Mareska, 1849–50; O'Rourke, 1875; Baer, 1876; Landa, 1916; Hülse, 1917; Jansen, 1918; Guillermin and Guyot, 1919; Burger, Sandstead and Drummond, 1945; Rosencher, 1946; Cardozo and Eggink, 1946; Ströder, 1947). It was their colour which betrayed some of the weaker defenders of Derry when they tried to escape by mingling with the country folk who were driven up under the walls by the enemy (Mackenzie, 1690).

Patchy pigmentation of the skin was recorded by Budzynski and Chelchowski (1916) in half-starved Polish townsfolk. This or similar pigmentation has been produced experimentally (Keys, Brozek, Henschel, Mickelsen and Taylor, 1945; Keys, 1946) and has become a recognized, if unexplained, feature of undernutrition (Laycock, 1944; Herrlich, 1947; Bigwood, 1947; Trémolières, 1947; Bansi, 1949). It may or may not have the same aetiology as the generalized pigmentation of the face and other exposed parts of the body that was recorded by Riehl (1917) and considered by him to be due possibly to undernutrition.

The texture of the skin has also attracted attention from at least the middle of the last century. Porter (1889), in describing the famine in Madras, stated that "usually the skin was dry and covered with scurf". Many references to skin changes in undernutrition were made during the first world war. Budzynski and Chelchowski (1916) noted that the skin was often dry. This was reaffirmed by Knack and Neumann (1917), and Petenyi (1918) made a point of the prevalence of a dry skin with desquamation of the legs in people who were undernourished. Park (1918) merely noted that "dermatitis" of the legs was common, but Burger (1919, 1920) again drew attention to the fact that the skin was sometimes dry and flaky, and that over the elbows it felt rough and hard. Gounelle, Raoul and Marche (1941) found the skins dry and scaly "avec desquamation furfuracée et croûtelleuse" and added that behind the elbows "l'aspect revêt souvent le type ostéacé". Williams (1933), a medical officer in the Gold Coast, introduced a syndrome into medicine for which she used the local term "kwashiorkor". It was characterized by signs of gross undernutrition and a dry skin which cracked into irregular patterns resembling crazy paving. The aetiology and nomenclature of this syndrome have been matters of dispute ever since. It was at one time thought to be one of the manifestations of pellagra. The skin changes appear to be exceedingly common in young children, not only on the

Gold Coast where they were first described, but also in other parts of Africa and in the West Indies, and have been well described and illustrated (Trowell, 1939–40; Trowell and Muwazi, 1945a,b; Waterlow, 1947). They are not confined to children, and very similar lesions seem to have been observed all over the tropics (Platt, 1945).

Goebel (1924) reported that when people were undernourished, and particularly in his opinion when they were short of fat, the skin became dry, and small superficial vesicles formed in it, which, he considered, originated in the sebaceous glands. Few others seem to have noted these superficial vesicles, but they were observed by Keys, Taylor, Mickelsen, Henschel and Brozek (1946) in the subjects who lived for months on insufficient diets designed to resemble those obtainable in Central Europe. The observations of Keys *et al.* suggest that the vesicles originate in the ducts of the sweat glands.

Soon after the first world war Bloch (1920–1, 1921), in writing about the xerophthalmia in Denmark whose origin in a deficiency of the fat-soluble vitamins was becoming recognized, mentioned that the infants sometimes had a dry and scaly skin. Actually, the association of keratomalacia with a dry scaly skin goes back much further than this. "Die Haut, besonders an den Extremitäten, war trocken, selbst rauh, wenig empfindlich, von glänzendem, schuppigem Aussehen, von zahlreichen feinen Falten durchzogen, nach Art der Haut alter Leute oder in der letzten Periode der Morphose" (de Gouvêa, 1883). Treatment with liver oil dates back further still and was regarded as a specific in the last century (Snell, 1876). Pillat (1929a, b) confirmed these findings and added that there was always conspicuous inactivity of the sebaceous and sweat glands, and that the skin was often covered with lesions resembling comedones. Frazier and Hu (1931, 1936) drew attention to similar abnormalities in skins and associated them with a vitamin A deficiency. They pointed out that spiny excrescences and hyperkeratosis pilaris were also part of the syndrome, and emphasized that true comedones were rare on a dry skin. Youmans and Corlette (1938) believed that dry horny spicules predominated in some people, acne-like lesions in others. Loewenthal (1933, 1933–4, 1935a, b), writing from Uganda, gave a clinical and histological account of papules which arose from the pilosebaceous follicles and which were microscopically identical with those of pityriasis rubra pilaris. There was some desquamation of the skin, and itching, and practically every case was curable by a daily dose of 1 oz. of cod-liver oil. Loewenthal ascribed these lesions to a deficiency of vitamin A. In 1933 Nicholls also described changes in the skins of prisoners, which were associated with neuritis, xerophthalmia or keratomalacia, and which he also considered were due to a vitamin A deficiency. These skins were dry and furfuraceous, and sometimes they were studded with papules that became dark in the course of time. Nicholls suggested that these papules were plugged and enlarged sebaceous glands and were presumably the comedones of Pillat and of Frazier and Hu. The condition, which Nicholls termed phrynoderma, was fully investigated by Rao (1936–7; 1937–8), who considered that the most conspicuous histological lesion was the plugging of the hair follicles with concentric flakes of shed epithelial cells.

There seems little doubt that all these authors were describing similar lesions, but there is not the same certainty about their aetiology. Goodwin (1934) considered that he had cured a London child with a dry scaly skin and pilosebaceous papules by giving cod-liver oil, and Rao (1938) cured two cases in India with a vitamin A concentrate, while Frazier, Hu and Chu (1943), whose

illustrations are very helpful, never seem to have been in any doubt that these lesions were due to a deficiency of vitamin A. Youmans (1943) also accepted this. Platt (1945) felt that the recent literature and his own experiences, which are well illustrated, established that phrynoderma was produced by a vitamin A deficiency, and Sefton (1946) would probably agree. Steffens, Bair and Sheard (1940) thought that they had produced hyperkeratosis of the skin and hair follicles by a diet deficient in vitamin A and cured it by giving the vitamin. Aykroyd and Krishnan (1936–7), however, and Aykroyd and Rajagopal (1936–7) thought that the clinical evidence made the association with vitamin A uncertain. Fasal (1944) thought that the hyperkeratosis observed by him in the Federated Malay States was not always cured by vitamin A and that it was advisable to give supplements of proteins and the B complex as well. Gross (1941) claimed to have cured hyperkeratotic eruptions and dry scaly skins by administering vitamins of the B_2 complex by mouth and liver extracts parenterally, and Moore's (1940) article illustrates again the difficulties and uncertainties of assigning a specific cause to these lesions. Salzmann and Hottinger (Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948) thought that the scaling, pigmentation, hyperkeratosis pilaris and other lesions observed and photographed by them in people who had been in concentration camps in south Germany were possibly due to vitamin A deficiencies, but they refused to commit themselves, and mentioned cold and trauma as alternative possibilities. To add to the uncertainty, the work on the vitamin A requirements of human adults (Vitamin A Sub-Committee, 1949) which was carried out during the war failed to demonstrate any connexion between hyperkeratosis and experimental vitamin A deficiency. The chemical and dermatological correlations have naturally been investigated, but attempts to demonstrate that persons with skin lesions of the above types had critically low vitamin A values in their sera have been unsuccessful (Peck, Glick and Chargin, 1943; Peck, Glick, Sobotka and Chargin, 1943; Weiner and Levin, 1943; Leitner and Moore, 1946; McIntosh, Moore, Keay and Cook, 1946), and Stannus (1945) wrote an article full of destructive criticism, which should be read by anyone interested in the subject.

The work on animals has not helped to establish the aetiology of these lesions. Moult (1943) considered that he had reproduced identical follicular changes in rats by depriving them of vitamin A, but there is no proof that the follicular lesions might not have been produced in other ways. Portmann (1927), for instance, thought that the lesions produced in the skins of his rats by a deficiency of Calories, of vitamin A or of vitamin B were all essentially the same. A fat-free diet has been shown to lead to hyperkeratosis in these animals (Williamson, 1941; Rothman and Felsher, 1946).

Many years before the existence of vitamin A was recognized, skin lesions had been described in association with scurvy. Jessner (1893), for instance, spoke of lichen scorbuticus. In 1918–19 Nicolau wrote an article on "une éruption folliculaire et perifolliculaire dans le scorbut". In the milder forms of these lesions the skin was covered with fine papules resembling goose-flesh, and in the severer forms with hard spiky excrescences projecting from dilated hair follicles. When these cornified plugs were picked out from the follicles an atrophic hair was found beneath. Histological examination showed that there was overkeratinization of the skin, particularly inside the mouths of the hair follicles, which, in consequence, were dilated and filled with laminated cornified flakes. The inner parts of the follicles were often atrophic and out of alignment. Nicolau also noted that the sebaceous glands were frequently atrophied and the erector

muscles hypertrophied. There can be no doubt at all that this was the lesion which was well described by Wiltshire (1919) at about the same time, and which has subsequently been redescribed (Scheer and Keil, 1934) and produced experimentally by ascorbic acid deficiencies (Crandon, Lund and Dill, 1940; Vitamin C Sub-Committee, 1948). In the later stages petechiae develop in and around the abnormal hair follicles, but apart from this there seems little to distinguish these changes from those that have been attributed to a deficiency of vitamin A. To illustrate the difficulty Théodorescou (1928) described lesions of the skin in a swineherd that he confidently attributed to scurvy, but the man's first symptom was night blindness, and this has made people attribute the changes to a deficiency of vitamin A.

A number of writers have commented upon the hair of the head in human undernutrition or malnutrition. Mori (1904) noted "die Kopfhaare glanzlos"; Platt (1945) spoke of "staring hair" and Salzmann and Hottinger (Hottinger *et al.*, 1948) described hair of this type in people who had been in German concentration camps and attributed it to trophic changes in the follicles. Wiltshire (1919) described overkeratinization, or an appearance of overkeratinization, of hair follicles not only over the body generally but also in the pubic region. Similar lesions in the scalp probably underlie the changes that have been detected clinically.

Lesions of the skin that are, to say the least of it, extremely like those described by Nicolau, Frazier, and others have frequently been noted, and it is most unlikely that they have always been due to deficiencies of vitamins A or C. Stannus (1911–12, 1913–14) described skins that felt prickly to the touch in some prisoners in Nyasaland. The hair follicles were plugged with hardened material, which projected as a tiny spike, and the follicles were surrounded by a dark areola. He termed this condition folliculitis. Riehl (1917) reported on a lesion resembling lichen pilaris in men, women and children, which, he considered, might be nutritional in origin. Whitfield (see Wiltshire, 1919) considered that undernutrition, particularly if it involved wasting, made the skin dry and rough and promoted changes in the follicles which he termed folliculosis. Samuel Pepys (1664) was one of the earliest writers to point out that cold and exposure tend to make the skin rough and prickly, and later authors have suggested that they cause the hair follicles to become dilated and packed with laminated keratinized material (MacCormac, 1926). Sequeira (1927) stated that these follicular changes were common in their milder forms, were not infrequently associated with some ichthyosis or xerodermia, and that the parts most commonly attacked were the extensor aspects of the arms and thighs. Projection and prominence of the follicles have been attributed to a poor peripheral circulation and held to be the result of the local malnutrition which ensues (Anon., 1947). Pemberton (1940) found that at least 5 per cent of a large group of schoolchildren and adolescents in Great Britain had hyperkeratosis follicularis and that many also had dry, rough skins. He considered that both these lesions were due to a deficiency of vitamin A or of fat, but subsequent work has not confirmed this. Cook, Davidson, Keay and McIntosh (1944) and McIntosh *et al.* (1946) made a dietary and clinical survey of Scottish schoolboys in the late winter and early spring of 1944, and found that 29 per cent of them had changes in the follicles which they took to be an early stage of the lesion described in vitamin A and C deficiencies. The authors, however, did not find that the administration of either vitamin had any effect on the lesions, and Stannus (1945) and Magee (1946) have endorsed these findings. Davidson, Wilcke, Fein and Reiner (1947) found

"follicular hyperkeratosis" among Viennese civilians, but surprisingly few signs of any vitamin deficiencies. Keys, Brozek *et al.* (1945) and Keys, Taylor *et al.* (1946) produced slight folliculosis and hyperkeratosis by keeping healthy young men on a diet that was adequate in vitamins but inadequate in Calories.

Thus, acne-like lesions, supposed to originate in the sebaceous glands, and overproduction of keratin, as evidenced by dryness and scaling of the skin and by the appearance of laminated cornified plugs in the hair follicles, have been attributed to vitamin A and vitamin C deficiencies and the claims have been supported by experiment. Similar changes have, however, been found in undernourished persons who were not suffering from these deficiencies. Overproduction of keratin has also been described in otherwise normal people who have been exposed to cold, and in others for no clear reason at all.

PRESENT OBSERVATIONS

Clinical

Some of the skin abnormalities that were seen in Wuppertal may be dismissed in a few words, for where no original observations or experiments have been made it is merely a matter of placing the facts on record. The curious pale colour, particularly of the face, was certainly common enough in Wuppertal. It was more noticeable in young men than in young women, but it was often masked by sunburn, particularly in prisoners of war who had just been repatriated from Russia. It was most noteworthy in the inmates of the civil prison at Siegburg in the summer of 1946. At that time the prisoners were very thin and undernourished, but they improved in the autumn in response to an increase in the rations, and by the end of the year most of them had lost their pallor. This pale appearance was not due to anaemia, for two of the palest civilian prisoners had 14·3 and 14·6 g. haemoglobin respectively in 100 c.c. of their circulating blood; nor did it seem to be due to a retention of bile pigment as it is in pernicious anaemia. Circulatory changes are a possible cause, which will be discussed later.

Patchy pigmentation was seen in a few repatriated prisoners of war. One man had a roughly oval brownish area on his face, which he said had originated while he was in Russia, and another, aged 48, had pigmented areas on the top of his bald head. This patchy pigmentation was the only abnormality of the skin that did not have a symmetrical distribution.

Only one man was seen with minute superficial vesicles of the type described by Goebel (1924) and by Keys *et al.* (1946). His skin, however, was not carefully investigated, for it was a very busy morning when he came to the clinic. He promised to return after a short visit to a farm in the country, but unfortunately he died there, and when this was discovered some time afterwards it was impossible to get a satisfactory account of his illness and death.

Roughness or flaking of the skin, particularly of the lower leg, was extremely common among the applicants for supplementary rations, the prisoners at Siegburg, and the prisoners of war repatriated from Russia. Sometimes the skin appeared almost normal with only a few branny flakes here and there, and these only noticeable when the skin had been rubbed. More typically the desquamation was obvious to the naked eye. The flakes were usually of about the same dimensions in any one patient, but their size might vary in different people from that of dust particles to pieces half a centimetre or more in diameter. Sometimes the flakes separated in such a way that the general appearance might

have been said to resemble crazy paving. Photographs of some of these skins are shown in Plates XII, XIII, XIV and XV.

Below the patella, and sometimes at the elbows, the skin often appeared to be thick, rough, and split transversely into deep cracks with sharp sides. The appearance was intensified by the presence of a little dirt, and this was not unusual. A photograph of such a skin is shown in Plate XVI. The skin illustrated belonged to a repatriated prisoner of war, and would have been regarded as showing advanced but by no means exceptional changes, but it should be explained that changes similar in type but of minor grades of severity were frequently seen among the applicants for extra rations, and sometimes in otherwise normal children.

Abnormalities in and around the hair follicles were also very common, and were usually accompanied by some flaking. The two changes tended to have different anatomical distributions, and one might appear without the other. Follicular changes were found in schoolchildren, undernourished civilian adults, civil prisoners and repatriated prisoners of war. They varied from minute firm excrescences to hardened spiky projections, which gave the skin a surface like a rasp. If mild, the changes were often confined to the extensor aspects of the arms and legs, and Plate XVII illustrates such changes in a German girl aged 8, who was believed to be well nourished. Their protean character made it difficult to define the clinical severity of these lesions. Some indication was obtained from the number of follicles involved in any one area, from the parts of the body affected, and from the size, hardness, and spikiness of the projections. Some of the most severe lesions were found among the civil prisoners at Siegburg in 1946, but advanced changes were met with in repatriated prisoners of war. The worst lesions were seen in a young civil prisoner whose entire body, except for his face, hands, feet, and penis, was involved. Many parts of his skin also showed exaggerated folding and elevations (Plate XVIII) which were regarded as being essentially similar to the transverse fissuring over the knees and elbows of the man shown in Plate XVI. Plate XIX illustrates the back of another prisoner in whom almost every follicle appeared to be involved, but to a relatively minor degree. Some acne-like changes were also present on this man's skin, but they were relatively uncommon in Wuppertal. Plate XX shows advanced hyperkeratosis pilaris on the buttock of a civilian prisoner at Siegburg, and this photograph also shows the loose folds of skin and subcutaneous tissue over the wasted glutei that were such a characteristic sign of undernutrition in some people. Plate XXI shows less severe hyperkeratosis pilaris on the arm of another civilian in Siegburg prison.

If many follicles were involved over any one area, and the degree of involvement was not great, an appearance resembling goose-flesh, i.e. a normal reaction of the skin to cold, was obtained, but if the plugs were sparse or large no one would have used this term to describe the skin. The larger spikes were sometimes reddish-brown in colour, and one repatriated prisoner of war, whose skin was almost normal when he was seen, volunteered the information that his skin had been covered with little red spikes at one period of his captivity. Sometimes the projecting parts between the folds and fissures appeared to be deeply pigmented, particularly over pressure areas (Fasal, 1944; Mitchell and Black, 1946). The man whose skin is illustrated in Plates XXII and XXIII was a repatriated prisoner of war, already well on the way to recovery, who stated that the skin over most of his body had been black when he was very undernourished.

With a lens the large spikes could be seen to project from hair follicles, and if the plug was picked out, a curled up hair often popped up like a jack-in-the-box,

with a piece of gummy material sticking to its tip. A collection of plugs was made from the man whose skin is illustrated in Plate XVIII, and a sufficient weight of them was obtained to enable an analysis to be carried out in duplicate by the micro-Kjeldahl method. This disclosed that they contained 11·8 g. of nitrogen per 100 g. of dry matter. The excrescences in this man were not materially changed by a hot bath every day for a week, and scrubbing half the body with soap and water did not make any real difference. The application of vegetable fat to the skin each day for several days softened the plugs but that was all.

The diet at Siegburg prison, and in Germany generally, excluded scurvy as a cause of any of these skin lesions, and no other signs likely to have been caused by a vitamin A deficiency were seen. Blood was withdrawn from eleven of the men with the worst skin lesions at Siegburg, and Dr. T. Moore kindly determined the concentration of vitamin A in the serum. The results varied from 138 to 236 I.U. per 100 c.c. for vitamin A (normal range 100–300 I.U. per 100 c.c.) and from 162 to 296 I.U. per 100 c.c. for carotene. The averages were 183 and 233 I.U. respectively. These figures seem clearly to show that these men were not suffering from a deficiency of vitamin A.

A number of the prisoners at Siegburg had chronic ulcers on their legs and a photograph of one of them is shown in Plate XXIV. These ulcers, which were not syphilitic, left on healing a brownish area of thin skin, and must have been exceedingly common among prisoners of war in Russia, for their legs were frequently covered with residual scars when they were repatriated.

Histological

Skin biopsies were performed on four civilian prisoners at Siegburg, four repatriated prisoners of war, and two civilian applicants for rations at the clinic at Barmen. In two of them specimens from two different parts of the body were obtained.

In six of these subjects follicular keratosis was the most conspicuous clinical feature, but some of the others also showed signs of hyperkeratosis as evidenced by thickening, roughening, or flaking of the skin. Of the two patients without conspicuous hyperkeratosis, one was the man aged 24 who said that he had been covered with little red spikes while in a Russian camp. At the time of the biopsy there was only very slight piling up around the hair follicles on the buttocks, and the piece of skin removed from the postero-lateral aspect of the thigh was considered to be normal in appearance though very damp; the patient sweated profusely on the slightest provocation (*McCance and Widdowson*, p. 1). No definite histological abnormality was detected in the sections of the skin of this patient, or in those of the only other patient without visible follicular changes. This was a young woman whose skin was described as "dry, shiny, not flaking, but rather rough" just below the knees, and as "glossy and flaky, very thin, almost like parchment" on the front of the shins. Biopsies were taken from both these parts.

All the biopsies were made after the skin had been cleaned with warm water and soap. The patients were given an injection of morphia or a proprietary omnopon scopolamine preparation subcutaneously, and no local anaesthetic was used until after the piece of skin had been removed for examination. Some procaine and adrenaline was then injected round the wound before inserting the stitches. The specimens were fixed in formol saline (4 parts formaldehyde, 96 parts 0·9 per cent saline). After fixation and before embedding, most of the specimens were examined under a binocular dissecting microscope. They were then

embedded in paraffin and sections were stained with Ehrlich's haematoxylin and eosin and sometimes also by Weigert's elastin and by van Gieson's stain.

When the unembedded specimens were examined under the binocular microscope, the opaque spiky excrescences of follicular keratosis were usually conspicuous, and in the specimens from the most affected skins were usually situated at the summit of low pyramidal protuberances separated by grooves which were apparently exaggerated natural skin grooves. Not all of the natural skin grooves were deepened, however: grooves of normal appearance were present over the surface of the protuberances. The whole surface was beset with these pyramidal protuberances, and the degree of undulation of the surface was decidedly greater than that in samples of apparently normal skin obtained during life for other pathological investigations, or at necropsy, and treated in the same way.

Examination of the stained sections at once revealed that the apparent thickening and undulation of the surface were not entirely, or even mainly, due to thickening of the epidermis. This is demonstrated by Plate XXV, which is a section of the skin shown in Plate XVIII. The horny layer of the epidermis usually did appear to be slightly thickened, but compared with the magnitude of the undulations the amount of thickening was insignificant, and it was no greater on the summit of the undulations than elsewhere. Sometimes the thickening appeared to be due to a loosening of the texture of the horny layer rather than to a real increase in the amount of keratin. The thickness of the horny layer varied more in different parts of the sections of the affected skins than in control sections of normal skin, and there was often some piling up of keratin in the furrows (compare Plates XXVI and XXVII). No definite abnormality was observed in the epidermis apart from the horny layer; the prickle cell layer was certainly not increased in thickness. The desquamation and scaliness, which were often so conspicuous clinically, were inconspicuous histologically. Thus the skin that is shown in section in Plate XXVIII was described at the time of the biopsy as " very flaky, without much obvious piling up around the hair follicles".

The most conspicuous histological abnormality was found in the follicles. Their mouths were distended with horny material (Plate XXVIII) in which the hair could sometimes be seen to have been cut two or more times, showing that it was twisted or coiled (Plate XXIX). Sometimes the undilated basal part of a follicle was cut twice in a single section (Plate XXX), suggesting that the tortuosity was not merely secondary to the follicular keratosis. Both hairs and hair follicles appeared atrophic. Even when erector muscles and distended mouths of follicles were abundant it was often difficult to find the basal part of any follicles, and it seems probable that many had disappeared. In the skin of normal people the bases of the hairs usually extend down into the subcutaneous fat (Plate XXVI); in these skins from undernourished people the follicles rarely reached down to the subcutaneous fat, and although this may have been partly due to an increase in the thickness of the non-fatty connective tissues of the dermis (see below), to a still greater extent it appeared to be due to the shortness of the thin, crooked follicles (Plate XXIX), which often did not even extend to the depths reached by the sebaceous glands. The sebaceous glands were rather poorly developed when compared with those of normal skin, but they appeared less atrophic than the follicles themselves; and as long as hair follicles were recognizable it was usually possible to find sebaceous glands.

No definite abnormality of the sweat glands was observed: they appeared normally abundant and well developed. Occasionally there was slight lympho-

cytic infiltration around them, as there also was round some of the distended hair follicles, but this cellular infiltration was inconstant and never more than slight.

Erector muscles were abundant even when few or no hair follicles were seen. Often they appeared to be considerably hypertrophied, especially in sections showing much undulation of the surface, but the range in their size in normal skin is so wide that it is impossible to be certain of this without measurement and statistical analysis. This has not been attempted, but nevertheless examination of the sections left a strong impression that the erector muscles were hypertrophied, at least in the more abnormal skins. This was one of the points made by Nicolau (1918–19).

The depth of the subcutaneous fat from the skin surface was apparently increased, as is shown in Table 1. The measurements recorded in the Table were

TABLE 1

A comparison of the depth of the subcutaneous fat from the skin surface in undernourished and in normally nourished people

Source of skin sample	Depth of subcutaneous fat from skin surface (mm.)	
	Undernourished people	Controls
Shoulder	5·0	3·0
	5·5	3·0
		3·0
Buttock	4·5	3·0
	4·5	3·0
	>4·0	3·5
Thigh	4·0	3·0
	4·5	1·5
		2·5
Knee	5·0	2·0
	4·0	2·0
	3·0	2·0

made on the cut surface of the specimens before they were embedded. After fixation, a clean cut was made through the piece of skin, and on the cut surface the line of demarcation between the yellow subcutaneous fat and the white dermis was clearly distinguishable. The distance of this line from the surface was measured to the nearest 0·5 mm. in all the biopsy specimens that were suitable. Similar measurements were made on control samples of skin obtained at routine necropsies in England on adult males aged 21–50 who showed no evidence of nutritional abnormality. The figures are too few to be entirely conclusive, but they are very suggestive of a retreat of the fat from the surface.

In the subcutaneous adipose tissue the cells were deficient in fat, as is shown by their relatively small size and their partial separation from one another (Plates XXXI and XXXII). A rough measurement of the mean diameter of the adipose cells was obtained by drawing the outlines of representative cells from each section at a magnification of × 440, and taking the mean of the largest and shortest diameters of each cell as the size of that cell. Each of the cells measured

was chosen from a different field, and its size was, as nearly as could be judged, representative of that of the cells in the particular field. The actual variation in the size of the fat cells in different specimens was large enough to make the technical inaccuracies of this rough method of measurement relatively unimportant. In twelve specimens of skin from undernourished people, the mean diameters of the fat cells were 25, 29, 27, 50, 39, 55, 43, 49, 55, 34, 36, and 50 μ respectively. In eight control specimens from normally nourished adults in England the corresponding figures were 82, 86, 64·5, 85, 62·5, 70, 90, and 56 μ. The sites from which the samples of skin came were as follows: *Undernourished subjects:* lumbar region 1, shoulder 2, buttock 2, thigh 2, knee 4, leg 1; *Controls:* buttock 2, thigh 1, knee 1, leg 1, arm 1, hand 1, scalp 1. Although these sites were not all directly comparable, they were sufficiently so to establish that the differences in the size of the fat cells were not due to differences in their site of origin.

DISCUSSION

It may be assumed that the undernourished people whose skins were examined in Germany were not suffering from a deficiency of vitamin A or C, but that their deficiency had been primarily one of Calories. Yet apart from the chronic ulcers, and even perhaps including them, the clinical and histological appearances of these skins do not seem to differ in any important respect from those that have been described by other people and attributed to a deficiency of vitamin A or C. Portmann (1927) came to similar conclusions about the skin lesions in rats caused by a deficiency of Calories, vitamin B or vitamin A, but this work was done before the vitamins had been so well differentiated as they are now. It is proposed, therefore, to regard all the manifestations of flaking and hyperkeratosis pilaris as essentially similar lesions, and to discuss the possibility of finding a common cause. The first point to bear in mind is that mild hyperkeratosis pilaris is quite common in otherwise normal children and adults, and the second is that cold and exposure can produce skin lesions in normal people that closely resemble, if they are not identical with, many of the abnormalities seen in undernutrition. This applies particularly to roughening, flaking, hyperkeratosis pilaris, and to enlarged erector muscles. This last should probably be regarded as a physiological response to continuous activity rather than a pathological change. Thus a section of skin taken from a very thin healthy man after several months of very cold weather showed follicles filled with laminated material, hypertrophy of the erector muscles and very small fat cells (41 μ in diameter). In starving people the skin has frequently been described as cold, and its pallor suggests that there must be a reduced amount of blood in the superficial vessels. It is probable that the lesions are often an exaggerated response of the skin of certain people to cold, or possibly to the reduced blood supply that accompanies it. It does not seem to matter whether the cold is applied to the surface or produced by a disordered metabolism, but if the essential lesion is a reduction in the blood supply this is easily understandable. The retreat of the fat from the surface may remove some of the normal heat insulation from the bases of the hair follicles and this may facilitate the changes that take place in them, but it is difficult to see how it can explain the flaking and other changes that occur nearer the surface. The role of vitamins A and C is still unexplained, but they may act either by sensitizing the skin to cold or by inducing vascular changes in the peripheral vessels which resemble those produced by semi-starvation.

An experimental approach is the only one likely to settle the matter, and so far identical lesions have not been produced in animals and it may be impossible to do so. The discovery of a suitable laboratory animal would undoubtedly aid progress. Most of the experimental work on man has been therapeutic, but skin lesions have been produced by a deficiency of vitamin C and of Calories. In spite of the acknowledged effects of vitamin A on epithelial structures, attempts to produce skin lesions in man by a deficiency of this vitamin have not been uniformly successful (Vitamin A Sub-Committee, 1949). To establish that cold or a vascular change is the final common cause much more work will be required on skin temperatures and peripheral circulations, but it may be possible to do this on clinical rather than experimental material, for there are plenty of the necessary kinds of undernutrition in the world.

SUMMARY

1. Undernourished people frequently had a peculiar pallor, and many of them a roughness and flaking of the skin, particularly of the lower leg, which suggested overproduction of keratinized cells (Plates XII, XIII, XIV and XV).

2. Sometimes the skin appeared fissured and folded and gave the impression of overkeratinization (Plates XVI and XVIII). The raised areas were occasionally pigmented, particularly over pressure points (Plates XXII and XXIII).

3. Plugs of hardened protein material often distended the hair follicles and projected as spikes (Plates XVII, XVIII, XIX, XX and XXI).

4. Chronic ulcers of the lower leg were not uncommon in young civilian prisoners (Plate XXIV). The legs of repatriated prisoners of war were often covered with their scars.

5. Histologically the chief abnormalities were the laminated plugs in the hair follicles, the atrophy and tortuosity of the hairs and follicles (Plates XXVIII and XXIX), and the hypertrophy of the erector muscles. The normal undulations were frequently exaggerated. The flaking was inconspicuous, and, apart from the follicles, there was usually no definite thickening of the keratinized layer of the skin.

6. In undernourished people the fat lay further from the surface than in normal people and the individual fat cells were small (Plates XXXI and XXXII).

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IV. RADIOLOGICAL OBSERVATIONS ON THE ALIMENTARY TRACT

by F. R. BERRIDGE

ABNORMALITIES in the radiological appearances of the small gut have been described in persons suffering from tropical sprue (Mackie, Miller and Rhoads, 1935; Snell, 1939; Drew, Dixon and Samuel, 1947), idiopathic steatorrhoea (Mackie, 1933; Snell and Camp, 1934; Mackie and Pound, 1935; Kuhlmann, 1939; Kantor, 1939, 1940; Hotz and Deucher, 1941), coeliac disease (Freise and Jahr, 1925; Fanconi, 1928; Gilbert and Babaiantz, 1934; Golden, 1936; Kantor, 1940) and kwashiorkor (Brown and Trowell, 1944; Kekwick, 1949). When in East Africa Kekwick also observed them in undernourished adult Bantus from all the East African provinces and in 45 per cent of native army recruits.

The abnormalities are broadly similar in these four diseases and consist of the following changes:

1. The transit time, that is, the time taken from the ingestion of the meal until the barium has entered the caecum, is abnormally long, but in the early stages or during recovery it may be shorter than the normal.

2. The calibre of the bowel may appear to be wider than in normal persons, especially in the duodenal and upper jejunal loops. Large differences in the calibres of neighbouring loops may be seen, most frequently in the middle third of the small intestine. At an early stage or during recovery, the bowel may appear to be narrower than in normal persons.

3. No rugae may be demonstrable in the duodenal loop and jejunum in severe cases, or the folds may be larger and more widely separated than the normal. Irregularities in width and spacing of the rugae are common.

4. Gas and fluid levels may be seen in the upper jejunum.

5. The shadow cast by the barium suspension appears to be less opaque than normal; it may be either homogeneous or mottled. This has been interpreted as indicating that the barium suspension has mixed with the intestinal contents.

6. Peristalsis is irregular and the barium moves in a jerky fashion. Parts of the bowel may appear to be without movement for as long as half an hour, but in the early stages or during recovery peristalsis may be brisker than the normal.

7. The barium column, instead of being continuous, is broken up into separate masses of barium, a change which is usually referred to as segmentation. No rugae may be visible at the margins of these segments, or the rugae may be large and irregular. Segmentation is most common in the middle third of the small gut.

8. After the main meal has passed on, small, irregularly distributed masses of barium may be left behind and may be seen between the "segments". This appearance is termed "flocculation".

These radiological abnormalities have also been reported in cystic fibrosis of the pancreas (Blackfan and May, 1938; Neuhauser, 1946), obstruction of the pancreatic duct (Snell, 1939) and obstructive jaundice (Gutzeit and Kuhlbaum, 1934). They have also been described in hookworm infestation (Krause and Crilly, 1943; Hodes and Keefer, 1945), intestinal allergy (Fries and Zizmor, 1937; Wing and Smith, 1942; Fries and Mogil, 1943), nephrosis (Pendergrass, Ravdin, Johnston and Hodes, 1936), and in a few other conditions that are not usually regarded as nutritional disorders.

MATERIAL AND TECHNIQUE

Seventy-eight undernourished persons, 70 men and 8 women, who attended the special out-patient department at the Städtisches Krankenhaus, Barmen, and 12 normal healthy English men, were given barium meals according to the technique described below. Fifty-four of the undernourished subjects had oedema at the time of examination; the remaining 24 had had oedema in the past year. The weight loss of the 78 subjects varied from 3 to 45 per cent of their "previous" weights, that is, the amounts stated by the subjects to have been their weights before the onset of undernutrition.

A second barium meal was given to some of the German men so that the action of atropine sulphate, carbachol B.P., prostigmin, adrenaline hydrochloride, pitressin and amyl nitrite on the small gut could be studied. These drugs were also given to 24 healthy men in England, but the amyl nitrite was replaced by glyceryl trinitrate. Sulphaguanidine and aneurin were also given to some of the German subjects and the small intestines were examined again afterwards. The repeat barium meals given to the German subjects were also used as an index of the constancy of the radiological appearances from one examination to another.

Advantage was taken of an investigation which was in progress (*Widdowson*, p. 313) to examine the alimentary tracts of 19 undernourished men before and after an eight-week period of unlimited food. The observations to be reported on the stomach and colon are largely based on the findings in these 19 persons, because the notes on the remainder of the cases were lost when a car was stolen.

The barium-meal technique was as follows: The subjects fasted for 12 hours before the examination, and 100 g. of pure barium sulphate suspended in 150 c.c. of normal saline were given to each person. A small amount of barium was first administered for the examination of the oesophagus and gastric mucosa. The whole amount was usually drunk over a period of about a quarter of an hour. If gastric evacuation was not proceeding normally at the end of this time, the subjects were placed on their right sides. This was only once unsuccessful. The gastric evacuation was considered efficient if the barium suspension produced a continuous stream as it entered the small intestine and coated the whole surface of the wall of the small gut. The subjects were screened at intervals until the barium reached the caecum. Films were taken according to the appearances observed on the screen.

RESULTS

Oesophagus

No abnormality was observed in the oesophagus in any of the subjects.

Stomach, Duodenum and Colon

The gastric rugae in the whole series did not appear to differ from the rugae of stomachs met with in everyday practice, but it is impossible to exclude some degree of mucosal atrophy using present radiological methods. The rugae of the stomachs of the 19 men who took part in the investigation described by *Widdowson* (p. 313) did not change as a result of the extra food. There was, therefore, no evidence that the rugae were abnormal.

The gastric evacuation times in the whole series of 78 undernourished subjects varied from 1 to 4·5 hours and averaged 2 hours. This is slower than the average of 1·5 hours (range 1–2 hours) taken for this meal by 12 healthy English subjects. The difference is significant statistically ($t = 2{\cdot}64$, $P = 0{\cdot}01$).

In 12 of the 19 men who received the unlimited food, the pylorus, observed when the subject was erect, was noted to be higher at the end than it had been at the beginning of the investigation. In 8 of these 12 and in 2 others there was a change in the shape of the stomach (Fig. 1), the greater curvature being flatter and the stomach wider. The alteration in the position of the pylorus and the flattening of the greater curvature can be explained by a heightening of the tone of the abdominal wall and an increase in the retroperitoneal fat. Thus, there had been some gastroptosis when the subjects were undernourished, which agrees with the findings of Heilmeyer (1946) that there was an increase in visceroptosis in Germany. He also observed that the "steerhorn" stomach had

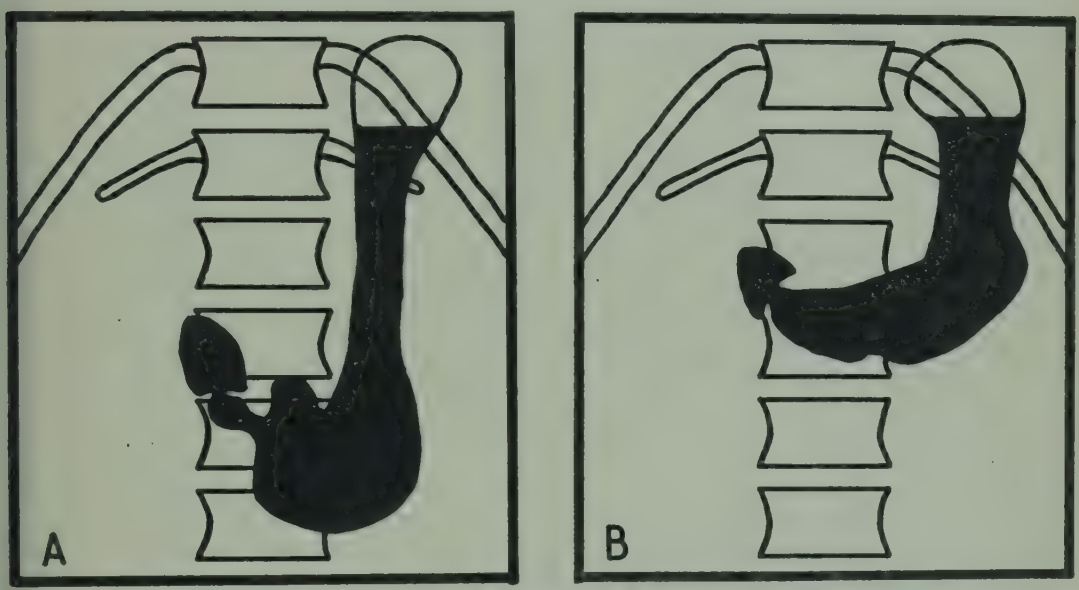

FIG. 1. Effect of an unlimited diet for a period of 8 weeks on the form of the stomach. A, before the period of unlimited food; B, at the end of period of unlimited food.

almost disappeared in Germany and had given place to the "fish-hook" form. In only one of the 19 subjects in this series was a steerhorn stomach found either at the beginning or the end of the period of unlimited food.

Nine peptic—three gastric, and six duodenal—ulcers were found in the 78 subjects. Two subjects had both gastric and duodenal ulcers, so that only seven subjects were affected in all. The incidence was thus 9 per cent. In 2,000 routine autopsies performed at the Mayo Clinic, Robertson and Hargis (1925) found evidence of past or present ulceration in 18·9 per cent. The incidence in the German subjects was low considering their ages, and gives no support to the suggestion of Dumont-Ruyters (1945) that the small amount of fat in the diet and the consequent prolonged state of emptiness of the stomach were possible factors in the higher incidence of peptic ulceration in Liége during the war. Uehlinger (Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948) found one peptic ulcer in his post-mortem examinations of 53 cases from concentration camps.

Duodenal ileus was present in six subjects. This is a surprisingly small incidence in view of the common opinion that loss of weight and visceroptosis predispose to it by allowing the superior mesenteric artery or the mesenteric pedicle to press upon the third part of the duodenum. In no instance was the ileus severe, nor did it ever give rise to more than a momentary delay in the passage of the barium.

The colons of 17 of the men who took part in the investigation on the effects of unlimited food were examined by the barium-meal method. Before the extra food was supplied the calibre of the colon and the position of the flexures were within normal limits. The transverse colon, however, tended to be lower than it usually is, and its most dependent part dipped into the true pelvis in 11 of the 17 subjects when they were in the erect position, and reached the brim in two others. The position of the flexures was unaltered by eight weeks of unrestricted diet, but the transverse colon was higher in 11 of the subjects, in 9 of whom the pylorus was also raised, and in 7 of whom the greater curvature of the stomach was flatter. It is probable, therefore, that the elevation of the transverse colon after eight weeks of full diet was secondary to the elevation of the stomach, or that the elevation of both was due to the same cause.

Small Intestine

The 78 undernourished persons who were given barium meals were divided into two groups, depending upon whether the small gut showed the radiological changes of flocculation and segmentation (Group 1, 42 persons), or not (Group 2, 36 persons). The clinical and laboratory findings were not quite identical in the two groups, and if all the evidence is taken together, the subjects in Group 1 may be regarded as having been slightly more undernourished than those in Group 2, although none of the differences was statistically significant. In view of the importance attached by Golden (1945) to the relation between the concentration of the protein in the serum and abnormalities in the radiological appearances of the small gut, it is interesting to note that there was no significant difference between the mean concentrations of the protein in the serum in the two groups, and that in one person in Group 2 the concentration of protein in the serum was only 4·0 per cent.

Situation of the coils. The coils of the intestine, especially those of the upper jejunum, were on the whole lower in the abdomen than those in normal persons.

Transit time. The transit time in the present study was taken to be the time from the ingestion of the barium meal until the head of the meal reached the caecum. It can only be an approximate figure as it was impossible to screen the subjects continually to find the exact time the meal entered the caecum. The transit time for the barium meal in 12 healthy English subjects varied from 1 hour 15 minutes to 4 hours and averaged 2 hours 40 minutes. The transit times in the series of the 78 undernourished persons varied from 1 hour 40 minutes to 11 hours 30 minutes and averaged 4 hours 40 minutes. In 44 of the 78 subjects it exceeded 4 hours, which was the longest transit time in the control group. The difference between the transit times for the healthy and undernourished persons was statistically significant ($t = 4{\cdot}3$, $P = < 0{\cdot}01$). There was no significant difference between the transit times of the two undernourished groups. The transit times could not be correlated with the concentration of the serum proteins, the basal metabolic rate, the oedema or the percentage loss of body weight. The body weight is not, however, an entirely reliable index of bodily wasting in undernourished persons (*Widdowson and McCance*, p. 165).

Calibre. In 30 persons in Group 1 and in 16 persons in Group 2 there were abnormal variations in calibre between neighbouring loops of the jejunum and upper ileum (Plates XXXIII and XXXIV). Dilatation of the jejunum was observed in 13 subjects in Group 1 and in 11 in Group 2 and nearly always affected the upper loops. One man had a grossly dilated small intestine. The dilatation of the jejunum was presumably due to a diminution of the tone of the bowel wall,

for it was also observed in the lower jejunum of some subjects when the gut was coated but not filled with barium. Repeated passive distension, however, was probably a contributory cause, since it was the upper jejunum which was most frequently dilated (Plate XXXV) and this is the part of the small intestine that is subject to a distending force extrinsic to the small gut, namely, the expulsive force of the stomach. The results of experimental starvation have shown that in rabbits (Weiske, 1897), guinea pigs (Lasarev, 1895), and cats (Böhtlingk, 1903) the percentage loss of weight of the stomach following starvation is considerably less than that of the intestines. It is probable, therefore, that the expulsive force of the stomach was little reduced in the German subjects.

Peristalsis. The frequency of the peristaltic waves appeared to be decreased in the jejunum if the subject had a long transit time, but the velocity of the waves appeared normal. They did not, however, travel as far as is normal in the small gut, but stopped, leaving the bowel in front of the bands of constriction wider and more elongated than the normal. Elongation was shown by separation of the rugae. These temporary hold-ups appeared to be responsible for the variation in calibre mentioned in the preceding paragraphs. Jerky movements of the intestinal contents resembling those found in patients with steatorrhoea were not observed. In the ileum the barium would sometimes remain almost immobile for as long as two hours, even after food had been given.

Rugae. Rugae were observed on the duodenal loop in all but one subject. In 18 of the subjects of Group 2 the jejunal rugae were perfectly normal, but in the subjects of Group 1 and the remainder of those in Group 2 they were nearly always somewhat larger than normal, that is from 2 to 4 mm. wide. In the subjects of the control group the width varied from 1 to 3 mm. The rugae also tended to be abnormally far apart, particularly in the lower jejunum (Plate XXXIII). This was noted in 28 of the subjects in Group 1 and in 18 of those in Group 2. The distance between the rugae was assessed when the bowel was coated but not filled with barium, so that the result should be independent of the filling of the gut (Plate XXXVI). In front of a wave of contraction, the rugae were more widely separated than in the small guts of normal persons (see above). In some cases, the widely separated rugae gave rise to a cog-wheel appearance, such as is seen in duodenal ileus, at the borders of filled jejunal loops. This wide separation might have been due to elongation of the gut or atrophy of the mucosa. The latter explanation implies that the bowel formed fewer rugae of large size rather than the usual number of small size. Both the width and spacing of the jejunal rugae were regular in the subjects in Group 2, but were at times irregular in those in Group 1. No abnormality was found in the rugae of the ileum.

Flocculation. Flocculation was observed in 24 of the subjects in Group 1. It was only considered to be present if the masses of barium, left behind after most of the meal had passed, were irregularly distributed (Plate XXXVII). Sometimes the barium ran freely over the surface of the gut and left these irregular flecks. Wide separation of the rugae allowed larger flecks of barium to remain in the crevices between them than are usually seen in normal persons, but these flecks were regularly distributed and were not classed as flocculation (Plate XXXVIII). It was in the upper jejunum that flocculation was most frequently observed, but it was also noted in the lower jejunum. The small masses were sometimes seen to move forward without altering shape and were presumably composed of clumped barium.

Segmentation. Segmentation was observed in 31 of the subjects in Group 1, most commonly in the lower jejunum and upper ileum, and in all but two cases

rugae were present at the margins of the segments. In some cases these rugae were irregular (Plate XXXIX). There was in general no peristalsis in the segmented areas and barium sometimes remained static in them for as long as half an hour. Palpation of the segments frequently caused the barium in them to move forwards. The width of the segments was usually greater than that of the empty coated bowel. Flocculation was observed without any segmentation in 11 subjects, and in 18 segmentation was seen without flocculation.

Worms. Ascarides were demonstrated in the small gut of 5 German subjects, but they were not accompanied by segmentation or flocculation.

Constancy of the intestinal appearances. Twelve persons whose intestines showed flocculation and segmentation were examined for a second time, when all but 3 of them still showed these changes. Of 11 subjects with initially normal small intestines, 3 showed flocculation and segmentation in their small guts at the second examination.

The Effects of an Unlimited Diet for a Period of Eight Weeks on the Stomach and Intestine

After eight weeks of unlimited food the mean gastric evacuation time of the 19 subjects was shortened from 1 hour 47 minutes to 1 hour 38 minutes (the difference was not statistically significant), and the mean small intestinal transit time shortened from 5 hours 9 minutes to 4 hours 8 minutes ($t = 2{\cdot}32$, $P = 0{\cdot}05$). Of 4 subjects whose intestines showed neither segmentation nor flocculation before the experiment, one showed these changes in the intestine at the end of it. Of the 15 subjects with initially abnormal bowels, in 5 the appearances became perfectly normal, in 1 they became worse, in 4 they were improved and in 5 they were unchanged. Although their general health was considerably improved by the good food, the subjects were not entirely restored to normal. Oedema was still present in 17 of the 19 men and achlorhydria in 12 out of the 16 who had had it initially. It would, therefore, have been unreasonable to expect that the appearance of the bowel would become uniformly normal in the same time.

The Absorption of Fat, and the Effect of Additional Fat on the X-ray Appearances of the Intestine

The German rations in 1946, when this investigation was being made, provided very little fat, and since so many of the changes observed in the intestines had been described previously in association with steatorrhoea it seemed desirable to determine whether the undernourished persons who were being studied radiologically were able to absorb fat quite normally. Six men were accordingly admitted to hospital and for three days they were given the ordinary hospital rations which provided 20·7 g. of fat per day. Carmine was given before breakfast on the first and fourth mornings and faeces were collected from the time the carmine appeared on the first occasion to the time it appeared on the second. Then 100 g. margarine, containing 88·9 g. fat, were added to the diet each day for three days, and the faeces were again collected for the three-day period corresponding to this higher fat intake. Carmine was again given on the seventh morning for demarcation of the faeces.

Over each three-day period, aliquot samples of all the food eaten were collected, thoroughly mixed, dried, and analysed for fat. The faeces corresponding to each three-day period were also well mixed, dried and analysed for total, split, and unsplit fat.

TABLE 1

The excretion of fat at two levels of fat intake

Subject	Low-fat diet			High-fat diet		
	Fat intake (g./3 days)	Fat excretion in faeces (g./3 days)	Fat in faeces as percentage of intake	Fat intake (g./3 days)	Fat excretion in faeces (g./3 days)	Fat in faeces as percentage of intake
X19	62·1	19·2	31·0	328·8	19·3	5·9
X26	62·1	3·4	5·4	328·8	6·9	2·1
B1	62·1	7·5	12·1	328·8	9·3	2·8
B40	62·1	20·1	32·4	328·8	17·4	5·3
B44	62·1	26·2	42·3	328·8	20·0	6·1
B62	62·1	12·6	20·2	328·8	17·5	5·3
Mean	62·1	14·8	23·9	328·8	15·1	4·6

Table 1 shows the intake and excretion of fat for each of the six men while they were eating the low-fat diet, and during the time they were receiving the additional fat. It will be seen that the absolute amount of fat excreted in the faeces was practically unchanged when the intake was increased by nearly 100 g. a day. It is quite clear, therefore, that these men were able to absorb fat without any difficulty whatever, in spite of the fact that their diets had contained so little for the past year or so. The excretion of fat, expressed as a percentage of the intake, was high during the low-fat period because most of the fat in the diet was derived from bread made from flour of high extraction (McCance and Walsham, 1948). When the intake was raised the fat derived from bread formed a much smaller percentage of the total dietary fat. Only 20–25 per cent of the "fat" in the faeces was in the form of fatty acids, whether the diet was high or low in fat. According to Harrison (1937) this is a very small percentage. This failure to split the fat, however, was probably due not to any abnormality in these men, but to the fact that the lipase in their intestines never had access to the fat in the whole-wheat bread.

The six men were examined radiologically before and after the high-fat diet. Three had normal small intestines at the beginning, and in two of them slight segmentation appeared in the jejunum afterwards. The gastric emptying times and intestinal transit times were not significantly altered. The other three men had abnormal small intestines before the additional fat was given. In one the X-ray appearance was unchanged on re-examination; another, who had previously had segmentation, showed flocculation but no segmentation; the third, whose jejunum showed flocculation at the beginning, had a normal small intestine at the end. Again the transit times and the gastric emptying times were not significantly changed. As has already been mentioned, identical results were not always obtained at two examinations of the same subject and, therefore, the alterations following the increase of fat in the diet were not really significant.

The Effect of Drugs on the Radiological Appearances of the Intestine

In view of the commonly accepted theory that the changes of flocculation and segmentation are due to damage to the intramural nervous system of the gut, it seemed important to determine whether the administration of drugs that act on the intestinal wall could abolish the abnormal patterns or even produce them in

normal people. The standard meal was given, but if there was insufficient barium left in the stomach to continue to fill the intestine during the time of action of the drug, more barium was given. The drugs were given after the bowel had been carefully scrutinized, and the subjects were screened and radiographs were taken at varying intervals afterwards. The drugs chosen were those acting on (1) the vagal nerve endings (atropine sulphate, carbachol B.P. and prostigmin); (2) the sympathetic nerve endings (adrenaline hydrochloride) and (3) the muscle wall (pitressin, amyl nitrite and glyceryl trinitrate). In addition, sulphaguanidine was given to two subjects by mouth, and others received aneurin. The German subjects are referred to as "abnormal" if the small gut showed the changes of flocculation or segmentation before the drugs were given, and as "normal" if it did not. Each of the drugs was also given to four healthy men in England.

Atropine sulphate. Elsom and Drossner (1939) gave barium meals to subjects to whom they had administered 0·43 mg. atropine sulphate subcutaneously, and noted slight intestinal dilatation.

Atropine sulphate (1 mg.) was given subcutaneously to four healthy controls in England and to four undernourished German subjects, two abnormal and two normal. In all the controls it produced an increase in calibre of the gut and a decrease in peristalsis. The forward progress of the meal was halted for periods of 30–40 minutes following the injection, and very slight flocculation appeared in the jejunum of one person. In the four German subjects, widening of the small gut and diminution of peristalsis were also observed following the injection. In the upper ileum of one normal man, after the atropine sulphate had been given, large smooth segments formed where none had been present before, and in the gut of another normal man flocculation appeared. Segmentation was present in the jejunum and ileum of two abnormal German subjects before the injection and these segments became very large after it. Thus atropine appeared to diminish the tone of the gut.

Carbachol B.P. An increase in the movements of the small intestine with the formation of local constrictions was observed radiologically by Fraser (1938) in three healthy students 15 minutes after the subcutaneous injection of 0·2–0·4 mg. of carbachol.

This drug (0·25 mg.) was given by intramuscular injection to four controls in England and six undernourished German men, two abnormal and four normal. Narrowing of the small gut and increased peristalsis were observed in all the controls. Following the injection, flocculation appeared in the jejunum of one control and segmentation with slight irregularity of the rugae in another. In the other two controls, the barium appeared blurred in the jejunum after the drug had been given, presumably because it became mixed with the intestinal secretions. The gut of the German subjects also became narrower and the movements increased after the injections, but the barium did not move forwards as a whole. Instead the back of the column was pushed onwards so that the gut at the head of the column became dilated. Slight flocculation appeared in the jejunum of one normal German man and irregular segmentation in the jejunum of another, where these appearances had not been present before. In one of the two subjects who showed segmentation in the gut before the injections the segmentation decreased and in the other it increased. Thus, carbachol did not consistently produce segmentation or flocculation in either the controls or the undernourished subjects, and its failure in the latter to initiate a general advance of the column of barium indicated a lack of balance in the movements of the gut as a whole.

Neostigmine methyl sulphate B.P. (*Prostigmin*). Ritvo and Weiss (1927) found that physostigmine, given orally or by subcutaneous injection, caused slow continuous wormlike movements in the human small intestine and an increase in its tone. The barium became divided into segments, some of which were dilated.

Prostigmin was given to four healthy men in England and to four German subjects, two abnormal and two normal. The calibre of the small gut became narrower in all of them and the movements increased. The controls received 0·5 mg. intramuscularly and in one of them segmentation was observed after the injection, the segments being very irregular and narrow. The same dose given to two normal Germans produced neither segmentation nor flocculation. In the two other German subjects whose bowels showed segmentation and flocculation, prostigmin in doses of 0·5 and 1·0 mg. respectively increased the segmentation and flocculation and made the rugae appear ragged. The subject who received 1·0 mg. prostigmin complained of abdominal colic 25 minutes after the injection and was given one injection of 1·0 mg. atropine sulphate. Thus, prostigmin also failed to produce segmentation and flocculation consistently, but appeared to make these changes worse when they were already present.

Adrenaline hydrochloride. Adrenaline hydrochloride B.P. (8 minims) was given subcutaneously to four controls in England and to four undernourished German subjects, two abnormal and two normal. It was followed by flocculation in the jejunum of the four healthy men. Peristalsis decreased in three of them 20 minutes after the injection had been given and remained so for 28–40 minutes. Slight segmentation was observed in the jejunum of one subject. In the two undernourished normal German subjects no change was observed following the injection. In one of the abnormal subjects flocculation increased in the jejunum and small segments formed in its lower part, and in the other segmentation in in the lower jejunum persisted unchanged, and flocculation appeared, together with some diminution of peristalsis. The most pronounced effect of adrenaline hydrochloride appeared to be the formation of flocculation.

Pitressin. Elsom, Glenn and Drossner (1939) noted hyperperistalsis and segmentation at barium-meal examination after the injection of 0·5–1·0 c.c. pitressin.

The intramuscular injection of pitressin in doses of 1–10 units produced increased peristalsis in the small guts of four healthy men in England and four undernourished persons, two abnormal and two normal, to whom it was given. The controls showed no other constant change; in one subject the gut became narrower after the injection. Following the injection of 10 units of the drug, a narrowing of the gut and the formation of narrow segments with irregular outlines were observed in the jejunum and ileum in two German men, one abnormal and one normal. In the small gut of one of the abnormal subjects there had been slight segmentation prior to the injection, but the outlines of these segments had been regular. The details of the rugae and, in places, the outline of the gut, were completely masked by the bizarre segmentation, which was unlike that seen in any other condition and resembled more than anything else the "amorphous calcium" seen in an atrophic Charcot's joint.

Amyl nitrite and glyceryl trinitrate. Amyl nitrite was given to four German subjects, two abnormal and two normal, but its effects were so transitory that it was decided to substitute glyceryl trinitrate when investigating the four control subjects subsequently in England. Linguets of glyceryl trinitrate (gr. 1/100) were given to four controls in England, and in three of them the

small gut increased in calibre and its peristaltic movements decreased; in two flocculation and segmentation appeared, but to a very slight degree in one. The rugae were unchanged. In the four German subjects the intestine relaxed slightly after the inhalation of amyl nitrite. Segmentation, originally present in two of these men, was not abolished, and appeared in another subject 10 minutes after the commencement of the inhalation. The rugae were unaltered.

Sulphaguanidine. Two German subjects were examined following the administration of 12 g. of sulphaguanidine daily for five days. One of these men had shown flocculation in the jejunum at a previous examination, and this was very much worse at the second examination. The jejunum of the other man had previously shown flocculation and segmentation, and this was not altered by the drug. Neither of these subjects had evidence of an infective enteritis, but it was thought possible that the intestinal changes might be associated with an abnormal bacterial flora, and that an alteration in the flora by sulphaguanidine might change the intestinal pattern.

Aneurin. According to Gershon-Cohen, Shay and Fels (1941), rats fed on a diet deficient in aneurin displayed diminished gastro-intestinal activity and varying degrees of dilatation of the whole gastro-intestinal tract. Elsom, Lewy and Heublein (1940) gave a healthy woman a diet providing what was thought to be one-third of the normal requirement of aneurin; it was assumed that the diet was equally deficient in the other vitamins of the B group. At the end of nine weeks on this diet, no abnormality was seen at barium-meal examination except increased calibre of the jejunal loops. The jejunum did not recover its original calibre after aneurin had been added to the diet for 18 days.

Aneurin was given to ten undernourished German subjects, either by mouth in dosages varying from 6 mg. daily for 14 days to 24 mg. daily for 6 days, or by intramuscular injection, 25 mg. per day, for periods of 6 days to 3 weeks. The small intestines were examined before and after the course of aneurin. Segmentation or flocculation was present initially in all of them. On re-examination the radiological appearances were more severe in three, unaltered in three, and improved in four, in only one of whom had the bowel become completely normal. The transit times were determined in five of the subjects and were shortened in two and lengthened in three. There was no correlation between the degree of improvement of the radiological appearances and the dosage level. The results in this series were too indefinite to give any support to the view that a lack of aneurin was the cause of the intestinal abnormalities, nor was there any clinical or dietary evidence of a deficiency of this vitamin.

DISCUSSION

It is probable from the evidence of experimental starvation in animals that the intestines of the undernourished subjects had wasted more than the stomachs. This would account for the functions of the stomach, so far as they can be determined radiologically, being almost within normal limits, whereas the intestines were definitely abnormal. The long transit times of the small intestine were in accordance with the general slowing down of the body function, but must have had a local cause. The separation of the rugae in the small gut was probably due to slight atony of the wall, which allowed the gut to elongate; the increased width of the rugae was probably due to the same cause. The occurrence of flocculation and segmentation in the gut of men who had practically no fat in their diet, but who could absorb fat quite normally, eliminated steatorrhoea as a cause or consequence of these abnormal intestinal appearances.

As has been mentioned already, in some of the subjects flocculation appeared to be due to small clumps of barium that had come out of suspension, whilst in others the barium ran freely as a liquid yet left these irregular flecks. It is interesting to note that King and Arnold (1922) observed an increased secretion of thick viscid mucus in the small gut of dogs after repeated epinephrin injections. They also observed the secretion of mucus after any stimulation that produced very active movements of the mucosa of the gut. Flocculation was observed after the injection of adrenaline hydrochloride in all the normal men to whom it was given in the present investigation, and both pitressin and prostigmin made the rugae appear very ragged in some of the German subjects. These observations suggested that the mucus might have been the cause of the irregular appearances of the rugae by intervening between the barium and the wall of the gut and thus preventing accurate delineation of the wall. In an attempt to prove this, samples of intestinal juice were aspirated through a Miller Abbott tube, but the estimations of the mucin in them were regarded as unreliable. The specimens, however, appeared to contain more mucus than samples from healthy persons in England.

Segmentation is to some extent linked with flocculation. Each mass of barium suspension ejected from the stomach passes rapidly through the normal jejunum leaving behind it a trail formed by the barium coating the mucosal folds and remaining in the valleys between them. When flocculation is present the masses that are passing down the gut appear to be separate from each other because there is no trail between them, thus giving rise to the appearances of segmentation. Exactly the same appearance has been observed in healthy persons when clumps of barium and mucus proceed through the jejunum at the head of the column (Plate XL) (Berridge, 1948), the admixture of mucus having deprived the barium suspension of the property of coating the bowel wall. Frazer, French and Thompson (1949) suggested that in the diseases associated with steatorrhoea, the abnormal intestinal appearances were due to an increased amount of mucin in the lumen of the gut, which caused the barium to clump together and come out of suspension. In support of this view, they found that the addition of 1 per cent lactic acid to the barium suspension produced segmentation in normal human intestines, and that lactic acid produced a secretion of mucus in the small gut of experimental animals and presumably also in the gut of human beings. We have observed that in some stomachs, especially those with some degree of hypersecretion, the barium rapidly separates from the suspending fluid and falls to the bottom of the stomach, leaving the supernatant fluid translucent to X-rays. This is presumably due to the gastric mucus which clumps the barium (Berridge, 1942). Segmentation is seen in the small gut of such persons since the barium and supernatant fluid leave the stomach alternately (Berridge, 1949).

It would thus appear highly probable that mucus alone can cause segmentation, but its clumping effect does not appear to be a complete explanation of the segmentation observed in all the undernourished subjects. In the small gut of these persons clumps of barium and mucus were sometimes observed at the head of the meal, and it was assumed that any mucus lying free in the lumen of the gut would cause such an appearance only in this part of the meal. Segmentation, however, was sometimes confined to a portion of the column some distance back from the head of the meal. It seemed unlikely, therefore, that increased mucus caused this segmentation. In Frazer *et al*'s. (1949) subjects, moreover, the bowel appeared to become narrower when segmentation had been induced,

whilst in the undernourished German subjects the calibre of the bowel either did not change or increased with the onset of segmentation. An explanation for this segmentation, therefore, was sought on the basis of the bowel movements.

In the lower two-thirds of the gut, the barium normally forms a continuous column, because the stronger movements at the upper end press the barium suspension against a resistance, which is partly anatomical (the narrowing calibre) and partly functional (the weaker movements lower down). It is possible that in the German subjects the movements of the gut were not strong enough to maintain the continuity of the column, and thus segmentation occurred in the middle third of the gut. It is suggested, therefore, that in the undernourished subjects there were two separate causes of segmentation, the clumping effect of mucus and weak bowel movements.

SUMMARY

1. The alimentary tracts of 78 undernourished persons were examined radiologically.

2. Evidence of slight gastric ptosis was found.

3. The gastric emptying times and the intestinal transit times were significantly longer than normal.

4. The bowel showed greater variation in calibre than is the case in normal persons, and it was frequently dilated.

5. The jejunal rugae were widely separated and on the large side of normal.

6. The small bowel of 42 subjects showed segmentation and flocculation.

7. The transit times of 19 men who were given unlimited food for eight weeks were slightly reduced by this treatment. The abnormal X-ray appearances tended to show an improvement.

8. The fat absorption of 6 undernourished subjects was found to be normal, and the addition of fat to the diet did not produce any significant change in the radiological appearance of the gut.

9. The action of certain drugs on the small intestine of undernourished subjects did not differ significantly from their action on healthy persons.

10. The flexures of the colon were normal in situation, but the transverse colon tended to be low and to rise after eight weeks of unrestricted diet.

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V. HEPATIC STRUCTURE AND FUNCTION

by SHEILA SHERLOCK (Beit Memorial Research Fellow) and
VERYAN M. WALSHE

IN recent years dietary deficiencies have been shown to alter the structure and function of the liver, but the work has usually been carried out on animals. The conditions prevailing in Germany in 1946 provided an opportunity of comparing these observations with the effects of undernutrition on liver structure and function in man. For this purpose clinical and biochemical investigations were made, and the histology of the liver was studied by means of the aspiration biopsy technique. All the biopsies were taken during the month of August, 1946, part of the laboratory work was carried out in Germany and the remainder at the British Postgraduate Medical School, London. A summary of the findings has already been published (Sherlock and Walshe, 1948).

SUBJECTS

Eighteen men who lived in Wuppertal and three prisoners in Siegburg gaol allowed themselves to be investigated, and some of the facts concerning them will be found in Table 1. The 18 citizens were admitted to hospital specifically for the observations. Their ages varied from 24 to 71 (mean 49) years. All had had hunger oedema, and in 15 this was still clinically detectable. Their loss of weight varied from 2 to 55 (mean 19) kg. Patients suffering from diseases known to influence hepatic structure and function were excluded. Three of the men suffered from benign symptomless hypertension, and one (No. 8) had a gastric ulcer. Three men had had infective hepatitis, two of them 24 and 26 years previously, the other (No. 14) in 1944 on the Russian front. No other subjects had a history of liver disease. The official rations at this time provided 1,300 Calories (*McCance and Widdowson*, p. 1). All the erythrocyte sedimentation rates were normal (*Thrussell and McCance*, p. 231).

METHODS

Aspiration hepatic biopsy. This was done by the method of Sherlock (1945). The sample of liver was divided into four pieces. One was placed in 10 per cent formol saline and one in absolute alcohol for routine histology. The others were used for the determination of glycogen and alkaline phosphatase.

Histological stains. Haematoxylin-eosin was used for the routine histology, and Best's carmine stain for glycogen. Reticulin was demonstrated by a modified Gordon and Sweets's (1936) silver impregnation method. Frozen sections were stained for fat using Sudan III. "Ceroid" was stained by a modified acid-fast stain (Pappenheimer and Victor, 1946). Iron was stained by a modified Perles's technique: the slightly warmed 20 per cent hydrochloric acid and 2 per cent potassium ferrocyanide was applied for 5–10 minutes; carmalum was used as counter stain. Alkaline phosphatase was demonstrated by Gomori's (1939) method.

Glycogen. The small piece of liver was divided into two for analysis in duplicate. The samples were dropped immediately into weighed centrifuge tubes containing 30 per cent potassium hydroxide, previously cooled in a mixture of ice and salt. The tubes were transported as quickly as possible to the laboratory in a vacuum flask containing ice and salt. There they were again weighed and the liver dissolved by warming. Analysis was performed by Good, Kramer and

Somogyi's (1933) method as modified by Walshe and demonstrated to the Biochemical Society in 1946. The samples weighed about 10–30 mg. Results are expressed in g. glycogen per 100 g. of wet weight of liver.

Liver alkaline phosphatase. Sherlock and Walshe (1947). Results are expressed in King-Armstrong units per g. of fresh liver.

Haemoglobin. Gibson and Harrison (1945).

Serum bilirubin. Haslewood and King (1937).

Bromsulphthalein excretion test. Helm and Machella (1942). The dose was 5 mg. per kg. body weight. Samples were taken at 5 minutes and 30 minutes after injection. Retention of more than 10 per cent of the standard was considered abnormal.

Faecal and urinary urobilinogen. The excreta were collected for 3 days. The urines were kept in dark glass bottles containing a little sodium carbonate and petroleum ether. The faeces were transferred from the bedpan into waxed cartons. A separate container was used for each 24-hour collection. Watson's (1936) method was used for the analyses, which were carried out every 24 hours.

Oral glucose tolerance test. The standard procedure was employed. Glucose (50 g.) was given to the fasting subject and the capillary blood sugar estimated by Haslewood and Strookman's (1939) method before ingestion, and 30, 60, 90, and 120 minutes afterwards.

Intravenous insulin tolerance test. This was made by the technique of Fraser, Albright and Smith (1941). Soluble insulin (0·1 unit per kg. body weight) was injected intravenously into the fasting subject. The capillary blood sugar was estimated before injection and at 20, 30, 45, 60 and 90 minutes afterwards.

Adrenaline sensitivity test. Adrenaline (0·5 mg.) was injected subcutaneously into the fasting subject. The capillary blood sugar was estimated before injection and 10, 20, 30 and 40 minutes later.

Serum alkaline phosphatase. King and Armstrong (1934).

Serum proteins. Micro-Kjeldahl technique (*Appendix*, p. 401).

Serum colloidal gold reaction. Maclagan (1944). The degree of precipitation was graded from 0–5.

Serum total and ester cholesterol. These were determined by the standard digitonin precipitation procedure.

Intravenous hippuric acid synthesis test. The intravenous technique of Quick, Ottenstein and Weltchek (1938), modified by Sherlock (1946), was used. The urine volume in every instance exceeded 60 c.c. If the excretion of hippuric acid was low, the patient's renal capacity was checked by a determination of his urea clearance. The values obtained were compared with those predicted by the formula of Scurry and Field (1943):—

Predicted hippuric acid excretion = (0·837 × surface area in sq. m.) − 0·163.

RESULTS

Clinical Features

A general account has been given of the way in which the patients were questioned and examined (*McCance and Widdowson*, p. 1). The group chosen for liver-function tests were specifically questioned in addition about the symptoms and signs likely to arise from hepatic dysfunction. All the subjects had voracious appetites. Flatulence, usually intestinal, was common and was probably due to the large quantities of vegetables in the diet. A history of purpura, epistaxis, haematuria, melaena, bleeding from the rectum or the passage of a dark urine was never obtained.

TABLE 1

Description of subjects

Subject No.	Age (years)	Occupation	Height (cm.)	Present weight (kg.)	Stated weight loss (kg.)	Liver palpable	Oedema of legs
1 (B57)	49	Metal worker	160	62	2	Yes	2
2 (B59)	52	Metal worker	164	50	18	No	2
3 (B68)	43	Metal worker	182	65	12	Yes	0
4 (B66)	59	Locksmith	170	62	15	No	2
5 (B62)	45	Labourer	176	63	24	No	3
6 (B71)	60	Weaver	162	52	30	No	0
7 (B72)	57	Gardener	167	51	17	No	2
8 (B69)	44	Machine worker	180	56	36	Yes	0
9 (B76)	44	Locksmith	170	60	12	Yes	3
10 (B14)	55	Unemployed	170	63	23	Yes	3
11 (B1)	41	Unemployed	166	72	8	Yes	2
12 (S27)	26	Prisoner	167	49	20	No	0
13 (S26)	29	Prisoner	157	39	10	No	0
14 (S28)	24	Prisoner	170	52	32	No	0
15 (B78)	66	Transport worker	162	50	27	No	3
16 (B80)	59	Booking clerk	175	63	55	Yes	2
17 (B79)	56	Odd-job man	170	45	21	No	3
18 (B82)	44	Unemployed	179	70	13	Yes	3
19 (B77)	54	Locksmith	167	59	11	No	4
20 (B83)	53	Night watchman	172	67	11	No	5
21 —	71	Retired	174	53	12	Yes	1

Details of the examination of the subjects are summarized in Table 1. It was obvious that the men had lost weight. Their complexion was sallow, but the mucous membranes were well coloured. Their skin was rather dry and very lax. They had no purpura nor had they any palmar hyperaemia or the vascular telangiectases characteristic of liver disease. Their nails were normal. Their tongues were clean and moist, and there was no visible atrophy of the mucosa. Their breasts were not hypertrophied nor were their nipples pigmented. Their abdomens were frequently protuberant and tympanitic on percussion. Only in one subject (No. 20) was free fluid clinically demonstrated. In nine patients the edge of the liver could be palpated; in six of these it could just be felt, and in the other three it extended 2–4 cm. below the right costal margin in the mid-clavicular line. In every case the edge was smooth, rounded and of rubbery consistence; it was not tender. There was no splenomegaly. Oedema of the legs was graded as described by *McCance and Widdowson* (p. 1), and the incidence is shown in Table 1. The clinical picture did not suggest hepatic disease or dysfunction.

Albumen was not detected in any of the urines, but a routine examination of 24-hour specimens by Schlesinger's alcoholic zinc acetate method revealed an excess of urobilinogen in all the samples tested. Values for the quantitative excretion of urobilinogen will be given later.

Faeces were formed, and their colour, although brown, was lighter than normal. They were not bulky, gassy or offensive, but they contained many undigested vegetable residues.

Histology

Sections of liver were obtained by aspiration biopsy from 20 patients. No cirrhosis, gross fatty change, necrosis of liver cells or microscopic haemorrhages were seen. The lobular pattern was always normal (Plate XLI), and in only two instances was there any excess of fibrous tissue in the portal tracts. There was no bile-duct proliferation or histiocytic infiltration of the portal tracts. The liver cells were of normal size. In one section there was apparently some narrowing of the liver-cell columns. There was no retraction of the sinusoidal wall from the liver cells. The cytoplasm, apart from the pigment changes to be described later, was normal. The cell nuclei sometimes varied conspicuously among themselves, and the larger ones often had very dark condensed chromatin (Plate XLII). Some of the cells contained two or even three nuclei, often joined together by narrow bands of nuclear material. Mitoses were not seen. The Küpffer cells were unexpectedly numerous throughout the lobule in ten of the sections, and they were sometimes plumper and larger than normal. An occasional polymorphonuclear leucocyte was to be seen in the sinusoids. The reticulin framework of the liver seemed to be normal. The two patients with slight fibrosis of the portal tract also had increased amounts of old black-staining reticulin in the portal tracts.

In 5 of the 20 sections very little glycogen could be demonstrated histochemically (Table 2); in the other 15 Best's carmine stain revealed on the whole a normal complement (Plate XLI). In the sections showing a deficiency of glycogen, little groups of liver cells sometimes contained normal quantities (Plate XLII), but these groups showed no constant anatomical distribution. In 8 of the 20 sections glycogen was visible in the nuclei of the liver cells (Plate XLIII). No relationship could be established between the histochemical amount of cytoplasmic glycogen and the presence of intranuclear glycogen (Table 2).

Liver samples from 17 subjects were frozen, cut and stained with Sudan III. There was a conspicuous absence of stainable fat. Scattered red droplets in the central liver cells were seen in only two of the sections, and traces of fat in four others. In the first mentioned sections a few of the Küpffer cells showed some fatty infiltration. The diameter of the drops was never larger than half that of the nucleus of a liver cell. The section with the most conspicuous fatty change is illustrated (Plate XLIV). A failure to demonstrate vacuoles in the alcohol and haematoxylin-eosin preparations was associated with the absence of fat in the sections stained with Sudan III.

In the haematoxylin-eosin preparations the cytoplasm of central and, occasionally, peripheral liver cells usually contained an excess of brown pigment. This was in the form of granules, often of angular shape, and was most obvious along the margin of the liver cell furthest from the sinusoid, that is, at the biliary pole of the cell. It resembled the "wear and tear" pigment normally seen in smaller amounts in the hepatic cells at the centre of the lobule. Attempts were made to identify the pigment more exactly. In frozen sections the granules did not take the Sudan III at all well (Plate XLV), and looked browner than the fat, which was frankly red. The pigment was again most conspicuous in the cells at the centres of the hepatic lobules. The weakly sudanophil property of the brown pigment was also demonstrated in paraffin-embedded sections. The pigment stained with fuchsin. A modified acid-fast staining technique failed to demonstrate ceroid pigment. The brown pigment in the central cells was therefore believed to be a chromolipoid (haemofuscin).

TABLE 2

Fasting blood sugar and hepatic glycogen

Subject No.	Fasting blood sugar (mg./100 c.c.)	Hepatic glycogen (g./100 g.)	Histochemical findings	
			Cytoplasmic glycogen*	Nuclear glycogen
1	90	2·9	+++	present
2	82	1·72	++	absent
3	106	1·6	++	absent
4	149	1·4	trace	present
5	106	—	trace	absent
6	95	1·3	trace	absent
7	89	2·0	+	absent
8	88	4·2	+++	absent
9	95	1·75	++	absent
10	90	2·02	++	present
11	87	—	++	present
12	57	1·5	+	absent
13	83	1·9	++	present
14	107	0·9	+	absent
15	93	0·8	trace	present
16	93	0·83	trace	absent
17	87	2·9	++	present
18	104	—	++	present
19	86	—	+	absent
20	91	—	—	—
21	—	—	++	absent
	Mean 94	1·8		
	S.E. mean (3·02)	(0·23)		

* The grading (0 – +++) has been adopted for cytoplasmic glycogen.

Apart from the chromolipoid, Prussian blue stains showed that some of the excess pigment in the liver was iron, and only 4 of the 20 aspiration biopsy sections showed a complete absence of haemosiderin; the amount present was very variable, and 5 of the sections contained traces only. Most of the iron lay in cells beside the portal tracts (Plate XLVI) and was in the form of discrete granules, although occasionally the cytoplasm was stained a diffuse blue. The granules were distributed along the biliary pole of the cells and bore no constant relationship to the nuclei, in which no iron was to be seen (Plate XLVII). There was no evidence that the cells which contained the iron were disorganized. The portal tracts on the whole were free from iron, but in two sections a solitary macrophage loaded with iron was found there. The Küpffer cells often contained haemosiderin (Plate XLVIII), usually in those sections where there was much parenchymal siderosis. There were exceptions, however, in which there seemed to be no relationship between the amounts of iron in the reticulo-endothelial cells and in the liver cells (Subjects No. 1 and No. 10). The Küpffer cell siderosis was most obvious in those sections which showed the greatest Küpffer cell proliferation, but it was not present in all the Küpffer cells in any one section, nor could a zonal distribution be established. In general the sections which showed conspicuous periportal cell siderosis also demonstrated the greatest increase of brown (chromolipoid) pigment in the centrally placed cells. Six

unstained sections showing the most conspicuous pigment were examined under ultraviolet light, but no fluorescence was detected.

Sections of liver stained for alkaline phosphatase usually showed that the enzyme was normally distributed (Table 3). In three of the sections (Nos. 9, 10, 13) the phosphatase activity was at the upper limit of that seen in normal subjects; one of these is illustrated (Plate XLIX). The hepatic cell nuclei showed the usual activity in the membrane and chromatin network. The dark cytoplasmic granules of haemosiderin and lipochrome produced a spurious appearance of phosphatase activity in the central and to a smaller extent in the peripheral cells, but the actual phosphatase activity of the hepatic cells was within normal limits. Alkaline phosphatase was always demonstrable in the walls of the central hepatic vein. The walls of the sinusoids varied in phosphatase activity: in eight sections they were not clearly marked out; in six, the walls of the central sinusoids were darkly stained, those in the pigmented zone somewhat less so (Plate L), and the extent of the sinusoidal staining in this group was at the upper limit of normal; the remainder of the sections showed the enzyme only in the walls of the sinusoids at the immediate entrance into the central vein. Küpffer cells associated with those sinusoids showing enzyme activity were darkly stained, and the occasional polymorphonuclear leucocyte in the sinusoids

TABLE 3

Serum and hepatic alkaline phosphatase

Subject No.	Microchemical estimation		Histochemical estimation			
	Serum (units/100 c.c.)	Liver (units/g.)	Grade*	Nuclei	Sinusoids	Excess granules
1	6·0	1·4	++	+	++	0
2	4·7	1·6	++	+	+	0
3	13·0	0·2	trace	+	0	0
4	3·5	1·2	+	+	0	0
5	4·5	0·2	trace	+	0	0
6	4·4	1·6	+	+	+	0
7	4·8	—	trace	+	0	0
8	6·7	0·4	trace	+	0	0
9	7·3	6·0	+++	++	++	0
10	9·0	8·8	+++	++	+++	0
11	8·6	—	++	++	++	0
12	4·7	6·6	++	++	+++	0
13	6·0	—	+++	+	+++	++
14	7·3	—	trace	+	0	0
15	6·9	1·95	+	++	0	0
16	6·9	3·4	++	+	0	0
17	6·6	1·6	++	++	++	0
18	8·3	—	trace	+	0	0
19	10·5	—	+	+	+	0
20	3·4	—	—	—	—	—
21	—	—	+	+	+	0
Mean	6·65	2·68				
S.E. mean	0·52	0·74				

* The grading (0 – + + +) has been adopted for alkaline phosphatase.

was black with phosphatase. In only one section did the bile canaliculi show patchy phosphatase activity. In the portal tracts the walls of the radicles of the portal vein and an occasional histiocyte gave reactions for phosphatase, but the hepatic arterioles, the small bile ducts, the lymphocytes and the connective tissue did not.

General Biochemical Investigations

Bile pigment metabolism. The findings are shown in Table 4. Haemoglobin was estimated in the blood of 14 subjects and was always less than 16 g. per 100 c.c. Serum bilirubin concentrations were always less than 0·7 mg. per 100 c.c., and no pink coloration could be detected on the addition of the diazo reagent and alcohol.

Bromsulphthalein excretion test. In 13 of the 20 subjects the dye was totally eliminated from the serum in 30 minutes. In the other 7 there was up to 7 per cent retention, which is within normal limits (Table 4).

TABLE 4

Haemoglobin, serum bilirubin, bromsulphthalein tests, and the urinary and faecal urobilinogen excretions

Subject No.	Hb (g./100 c.c.)	Serum bilirubin (mg./100 c.c.)	Bromsulphthalein (per cent retention after 30 min.)	Urinary urobilinogen (mg./24 hr.)				Faecal urobilinogen (mg./24 hr.)			
				Mean	Day of test			Mean	Day of test		
					1	2	3		1	2	3
1	12·8	0·5	6·7	0·7	0	0	2·1	1	0	0	4
2	10·3	0·5	4·0	0·4	0	0	1·4	23	0	30	40
3	14·5	0·5	0	1·3	0·6	1·5	1·7	72	0	203	14
4	13·3	0·5	0	3·3	1·8	4·5	3·7	12	0	4	31
5	14·8	0·5	0	1·4	0·8	1·3	2·1	25	0	71	5
6	12·3	0·5	0	1·0	0·7	1·5	0·8	9	14	5	7
7	13·3	0·5	0	2·5	0·9	2·8	3·8	33	24	60	15
8	13·8	0·5	0	2·5	0·5	3·0	4·0	5	0	0	16
9	13·5	0·5	0	4·1	1·3	3·8	7·3	15	0	20	25
10	13·6	0·6	5·0	3·8	8·1	1·0	2·3	11	8	17	9
11	12·0	0·6	0	3·4	4·8	3·1	2·2	6	4	2	11
12	—	0·5	3·4	—	—	—	—	—	—	—	—
13	—	0·5	1·4	—	—	—	—	—	—	—	—
14	—	0·5	0	—	—	—	—	—	—	—	—
15	10·6	0·5	5·5	5·5	7·6	2·3	6·5	17	36	0	16
16	13·9	0·6	0	5·7	7·3	4·9	4·8	12	0	0	35
17	9·4	0·6	0	5·8	9·5	2·1	—	13	18	20	0
18	13·2	0·5	2·0	3·9	0·2	2·4	8·5	44	29	32	75
19	10·5	0·5	0	2·4	2·1	0·6	4·6	34	11	47	45
20	10·9	0·5	0	3·3	1·4	2·7	6·7	24	0	7	65
21	—	0·5	—	—	—	—	—	—	—	—	—
Mean	12·5	0·52	1·4	3·0				20·9			
S.E. mean	0·74	0·005	—	0·16				4·2			

Urinary and faecal urobilinogen. Only 6 of the 17 subjects excreted normal amounts of urobilinogen in their urine on all three days of the test. The other 11 excreted 4 mg. or more of urobilinogen on one or more of the three days. The

patients tended to pass large volumes of urine, probably because of the amount of soup consumed and the elimination of extracellular fluid. The actual concentration of urobilinogen per 100 c.c. of urine was therefore sometimes normal, although the 24-hour excretion was increased.

The mean wet weight of the faeces for each of the three days of collection was 78, 82, and 150 g. The daily excretions of urobilinogen were low, which probably accounted for the pale brown colour of the stools already mentioned. Both the

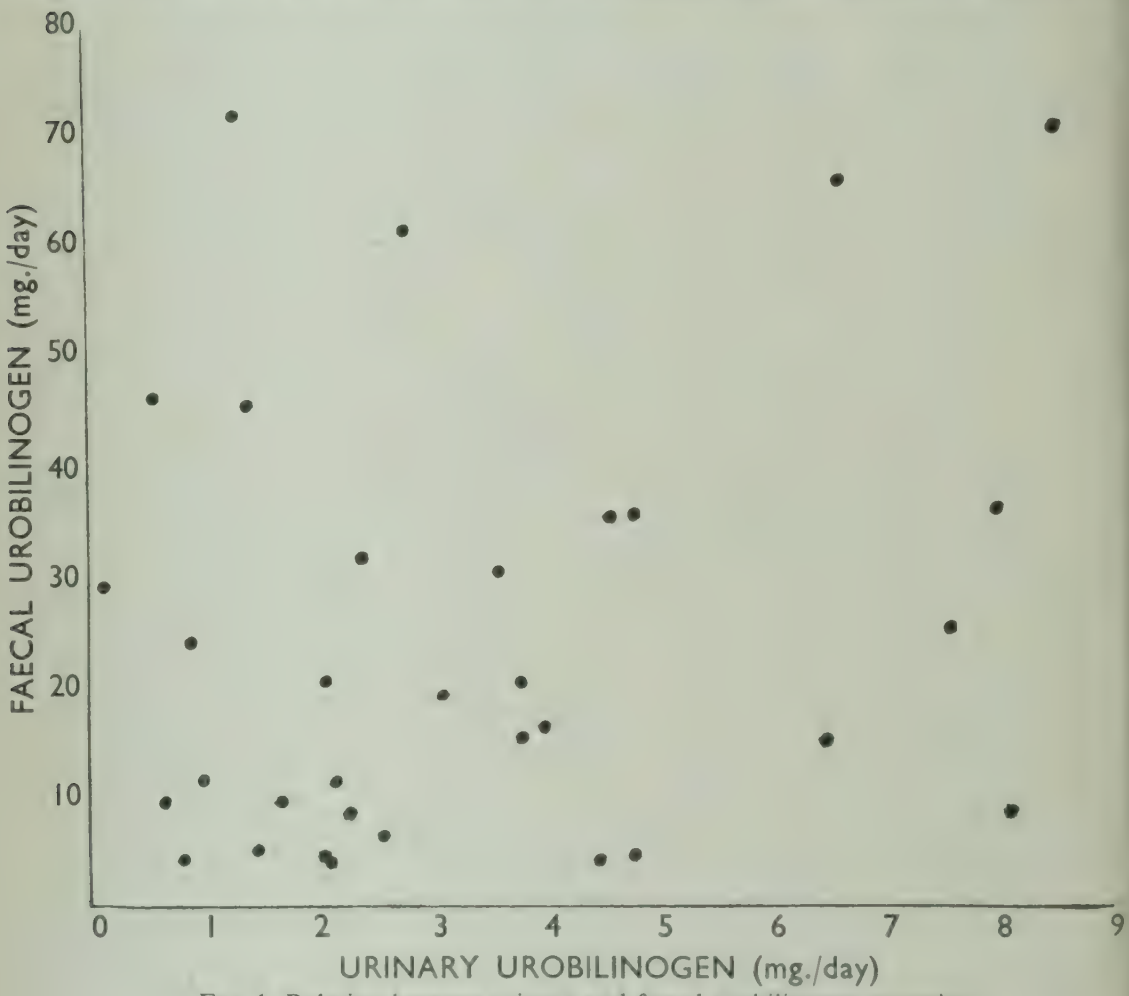

FIG. 1. Relation between urinary and faecal urobilinogen excretion.

total excretion and the concentration of urobilinogen per 100 g. faeces were low. An output of 40 mg. per day is generally taken as the lowest limit of normality, and 10 of the 17 subjects excreted less than this on all three days of the experiment. Only 2 had a mean excretion of over 40 mg. per day and the highest mean was only 72 mg. per day.

There was no apparent correlation between the daily excretions of urinary and of faecal urobilinogen (Fig. 1), or between the haemoglobin concentration and the mean excretion of urinary urobilinogen for the three-day period (Fig. 2). A comparison was made between the amount of iron demonstrated in the biopsy sections and the urinary urobilinogen excretion and the haemoglobin concentration, but in this small series there appeared to be no relation between them.

Carbohydrate metabolism. The findings are shown in Table 2. The fasting blood sugar was estimated in 20 subjects and, apart from one low value (No. 12)

and one rather high figure (No. 4), the values were within normal limits. In subject No. 4 the estimation was repeated on two subsequent occasions and the concentrations were 98 and 111 mg. per 100 c.c.

The hepatic glycogen concentration was estimated quantitatively in 15 subjects who had fasted overnight, and there was much variation in the results The values were compared with those obtained on 13 control subjects, who

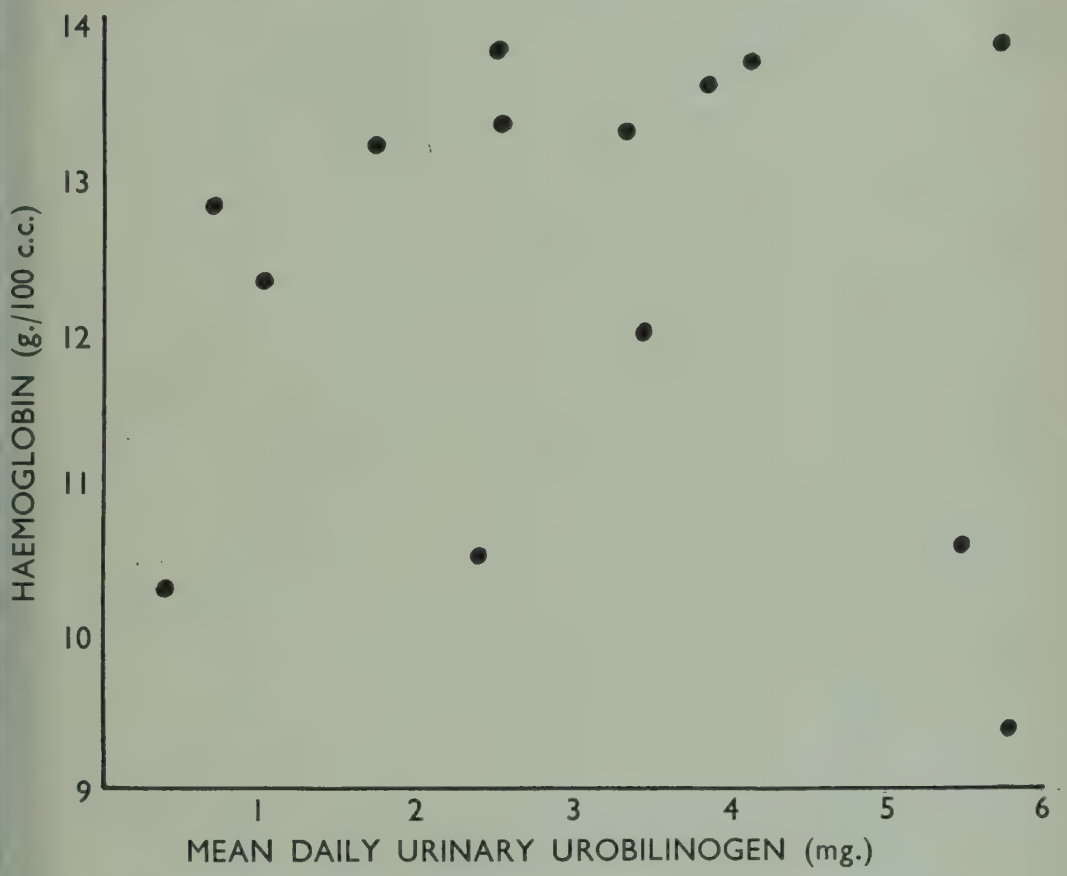

FIG. 2. Relation between haemoglobin concentration and urinary urobilinogen.

were British hospital patients suffering from diseases believed not to involve the liver. Although the mean value was lower in the German group (1·8 g. per 100 g., range 0·8–4·2) than it was in the British group (2·19 g. per 100 g., range 0·95–4·1), statistical analysis showed no significant difference between the means. No correlation could be established between the concentration of hepatic glycogen and either the fasting blood sugar (Fig. 3) or the loss of body weight. Although the histological method is generally recognized to be of little quantitative value, a comparison of the results obtained by it and by the microchemical estimations of glycogen showed that, with one or two exceptions, the two methods agreed reasonably well (Table 2).

Oral glucose tolerance tests were performed on 6 subjects (Fig. 4), and gave fasting values within normal limits. After the ingestion of 50 g. glucose the blood sugar took 30 or 60 minutes to reach its peak, which was at least 37 mg. per 100 c.c. above the fasting value. The blood sugar in every instance was below its resting value within 90–120 minutes. The oral glucose tolerance tests were therefore normal.

Intravenous insulin tolerance tests were performed on 5 subjects (Fig. 5); the fasting blood sugar values were within the normal limits. The intravenous injection of 0·1 unit of soluble insulin per kg. body weight did not produce any

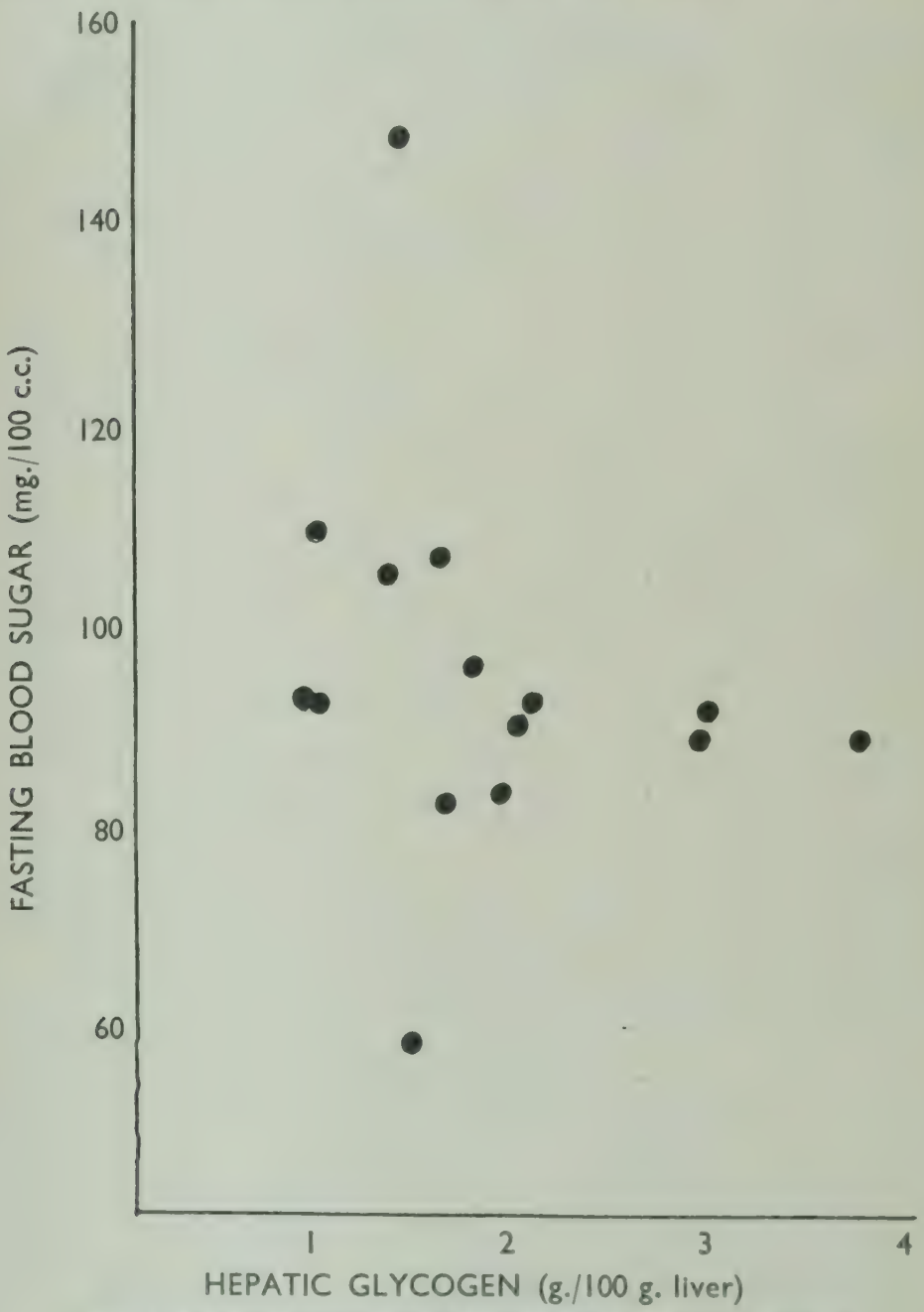

FIG. 3. Relation between fasting blood sugar and hepatic glycogen.

general reactions. The lowest blood sugar was recorded once at 20, twice at 30, and twice at 45 minutes after the injection. The last sample of blood was taken 90 minutes after the injection, and by this time the concentration of sugar was within 5 mg. per 100 c.c. of the resting value in 3 patients and 15 mg. and 14 mg. per 100 c.c. respectively, below this level in the other two.

Adrenaline sensitivity tests were performed on 6 subjects (Fig. 6). The fasting blood sugar values were within normal limits. The subcutaneous injection of 0·5 mg. adrenaline hydrochloride in one man caused transient palpitations, but

there were no reactions in the other 5 subjects. The maximum rise in blood sugar occurred between 10 and 30 minutes after the injection. In 5 subjects this rise was at least 29 mg. per 100 c.c., but in the sixth (No. 4) there was a very poor response to the adrenaline, for the highest blood sugar, which was not recorded till 40 minutes after the insulin had been given, was only 10 mg. per 100 c.c. above the initial level. This subject had a normal oral glucose tolerance test.

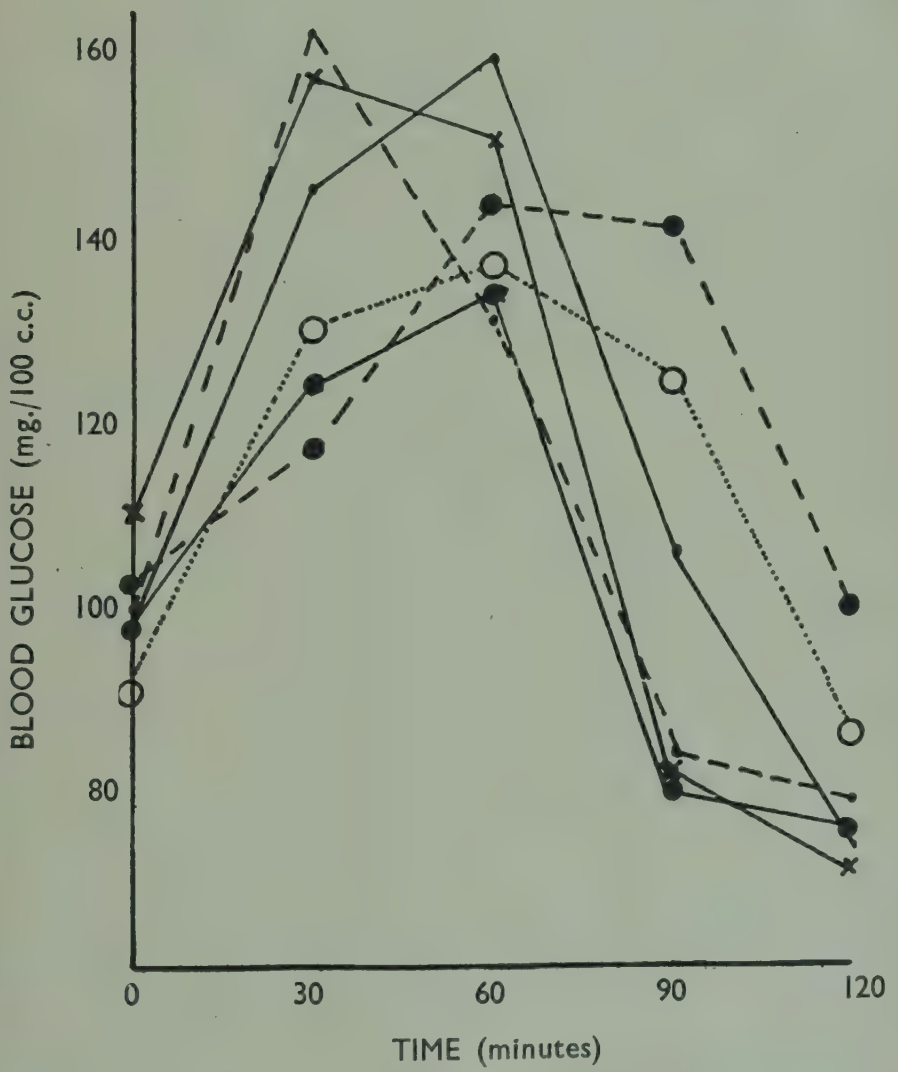

FIG. 4. Oral glucose tolerance tests. ×——×——× Subject No. 4, ●——●——● No. 7, O·····O·····O No. 9, •——•——• No. 15, • — — • — — • No. 16, ● — — ● — — ● No. 19.

Alkaline phosphatase studies. The activity of the alkaline phosphatase in the serum was estimated in 20 subjects and all the values were within normal limits. Hepatic alkaline phosphatase was estimated quantitatively in 13 subjects, and showed much variation from one subject to another. The findings have been compared with those in 12 British hospital patients. The average in the German group was slightly higher (2·68 compared with 2·40 units per g.), but there was no significant difference between the means. There was no correlation between the activity of the enzyme in the serum and in liver cells, between the loss of body weight and the activity of the liver enzyme, or between the microchemical

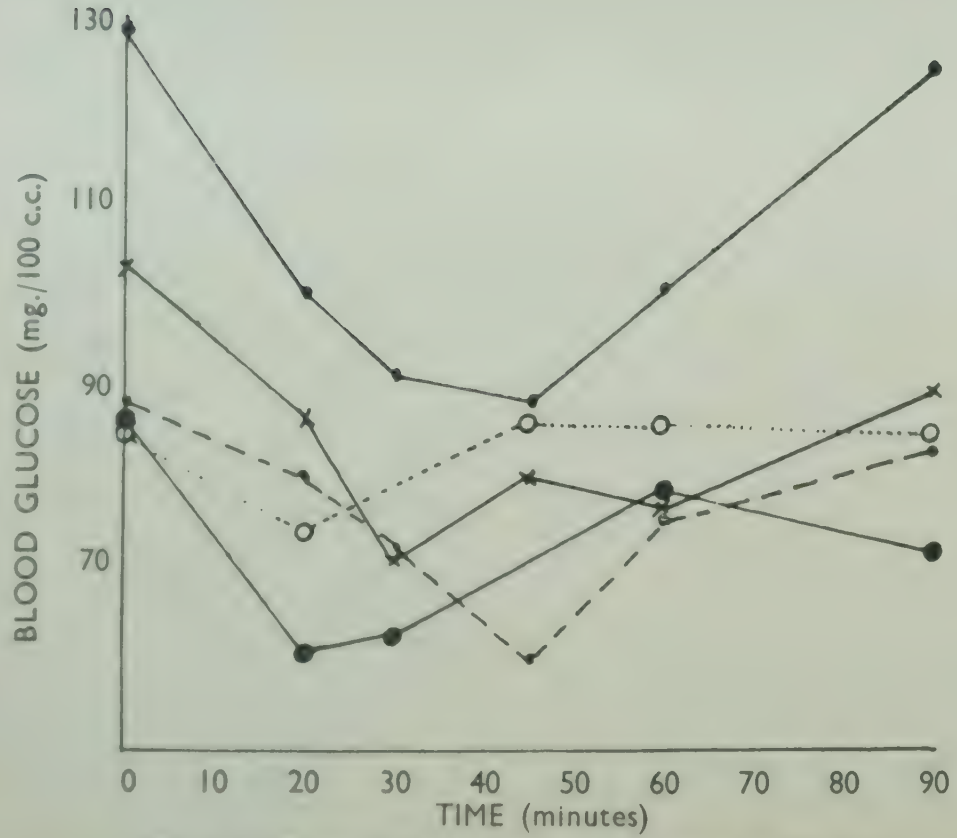

FIG. 5. Insulin sensitivity tests. ●——●——● Subject No. 7, O·····O·····O No. 9, • — — • — — • No. 10, •——•——• No. 15, ×——×——× No. 16.

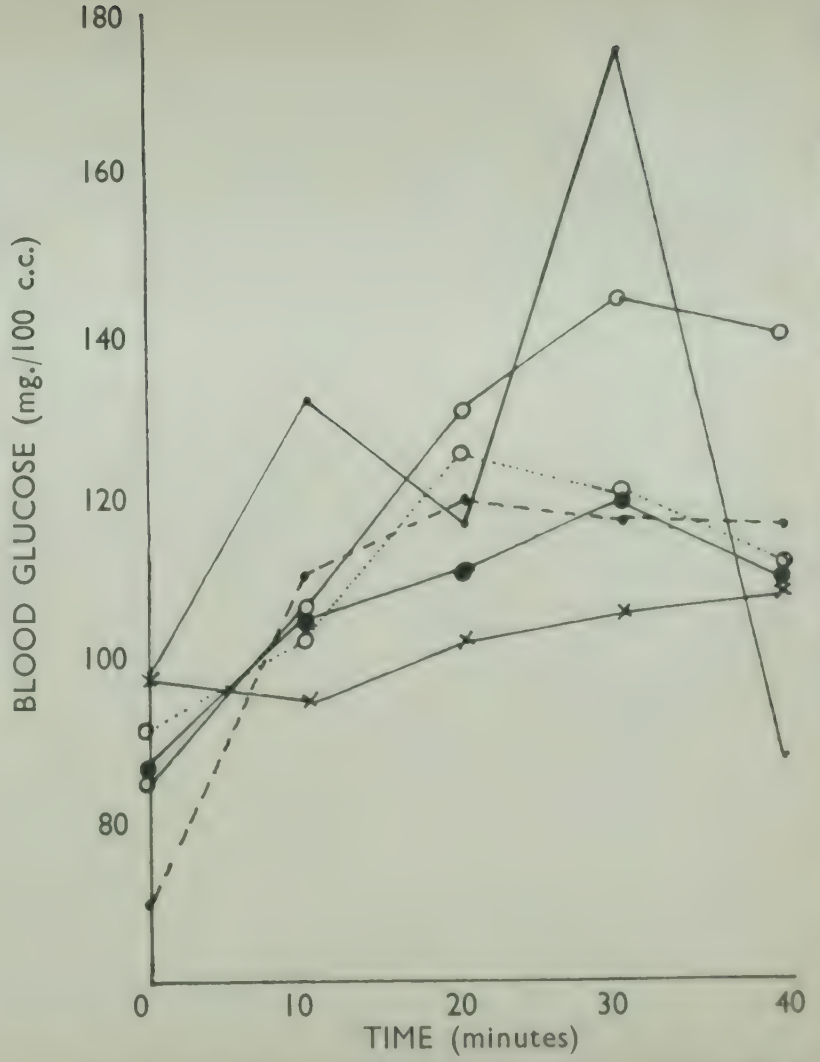

FIG. 6. Adrenaline sensitivity tests. •——•——• Subject No. 2, O——O——O No. 3, ×——×——× No. 4, O·····O·····O No. 6, ●——●——● No. 7, • — — • — — • No. 8.

quantities of alkaline phosphatase and of glycogen in the liver. A comparison of the histochemical and microchemical findings for liver phosphatase, together with the microchemical findings for serum phosphatase, is given in Table 3.

Serum proteins. The values for albumen, globulin and total proteins are shown in Table 5. It should be noted that 8 of the 20 subjects had total serum

TABLE 5

Serum protein and total and ester cholesterol concentrations, and the serum colloidal gold reaction

Subject No.	Serum protein (g./100 c.c.)			Serum colloidal gold reaction*	Serum cholesterol		
	Total	Albumen	Globulin		Total (mg./100 c.c.)	Ester	
						mg./100 c.c.	Per cent total
1	5·5	3·3	2·2	0	164	—	—
2	4·8	3·1	1·7	5	200	63	32
3	6·7	4·9	1·8	0	80	—	—
4	5·4	3·8	1·6	1	182	52	29
5	5·1	3·6	1·5	1	110	57	52
6	6·6	4·5	2·1	0	150	45	31
7	6·0	4·4	1·6	3	110	30	23
8	5·9	4·0	1·9	0	188	115	61
9	4·6	3·1	1·5	0	290	—	—
10	6·7	3·7	3·0	0	145	—	—
11	6·5	4·4	2·1	0	210	125	60
12	6·5	4·5	2·0	1	227	93	40
13	5·9	3·3	2·6	0	132	—	—
14	5·5	3·6	1·9	0	123	44	36
15	5·0	3·5	1·5	0	230	47	21
16	6·0	3·9	2·1	0	101	—	—
17	5·3	3·7	1·6	0	91	—	—
18	5·6	3·6	2·0	4	250	—	—
19	4·7	2·7	2·0	1	193	—	—
20	3·8	2·3	1·5	1	147	115	78
Mean	5·6	3·7	1·9		166	71·5	
S.E. mean	0·25	0·12	0·07		12·6	9·7	

* The degree of precipitation was graded from 0–5.

protein concentrations below 5·5 g. per 100 c.c. Tests were made in the recumbent position. Despite the lowering of the total values the albumen/globulin ratio lay between 1·3 and 2·7, that is, within normal limits. There was no correlation between the loss of weight or the peripheral oedema found clinically and the serum protein levels.

Serum colloidal gold reaction. This test was performed on sera from 20 subjects and the results are shown in Table 5. In 17 there was no precipitation (grade 0 and 1), in one there was slight precipitation (grade 3), and in 2 there was a strongly positive reaction (grade 4 or 5). The results could not be correlated with the loss of weight, the extent of peripheral oedema or with the concentrations of total protein, globulin or cholesterol in the serum.

Total and ester cholesterol in the serum. The results obtained are shown in Table 5. The total cholesterol concentration was extremely variable, low values

being encountered more frequently than high ones. In 7 of 20 subjects the serum cholesterol was less than 140 mg. per 100 c.c.; in 5 it was greater than 210 mg. per 100 c.c. There appeared to be no correlation between the weight of the subject when the test was made or the amount of weight that he had lost and the serum cholesterol concentration. In 16 of the subjects it was possible to compare the serum cholesterol concentration with the basal metabolic rates but no correlation could be established, nor did it appear that the presence of the fat in the liver cells and the serum cholesterol concentration were related.

The ester cholesterol concentration was estimated in 11 subjects and gave a wide range of values (Table 5). The mean value was low, being less than 60 mg. per 100 c.c. in 6 of the subjects. The percentage of ester in the total cholesterol was often reduced, and in 6 of the 11 subjects it was less than 40.

Intravenous hippuric acid synthesis test. The test was performed on 11 subjects and the results are shown in Table 6. The volume of urine passed in the hour

TABLE 6

Intravenous hippuric acid synthesis test

Subject No.	Surface area (sq. m.)	Volume of urine (c.c./hr.)	Excretion of hippuric acid (g./hr.)*	Predicted excretion of hippuric acid (g./hr.)*
2	1·53	156	1·01	0·93
3	1·84	75	1·10	1·14
4	1·72	194	1·04	1·06
6	1·63	156	1·05	0·99
7	1·56	138	0·79	1·02
8	1·71	78	1·10	1·05
9	1·70	74	0·94	1·04
10	1·76	64	0·77	1·11
15	1·51	550	0·83	0·92
16	1·78	130	0·87	1·12
19	1·63	92	0·89	0·99

* The hippuric acid excretion is expressed in terms of sodium benzoate.

always exceeded 60 c.c., and the excretion of hippuric acid, expressed as sodium benzoate, was always more than 0·76 g. The mean value for the group was normal. In view of the conspicuous loss of weight, the hippuric acid (as sodium benzoate) excreted per sq. m. body surface was estimated and compared with the predicted excretion obtained from the formula of Scurry and Field (1943). Only in three instances was the observed excretion less than the expected by more than 0·1 g. There was no relation between the concentrations of total protein, albumen or globulin in the serum and the excretion of hippuric acid. Patients who excreted normal amounts often had low serum proteins.

DISCUSSION

It has been extremely difficult to compare our findings with many of the recent accounts of malnutrition among released prisoners of war. The prisoners often had some complicating disease or infection, particularly if they had been in the Far East, and they were often not examined till some little time after their release. Difficulties of this kind did not arise to the same extent among European

civilians. It must be understood that the present Report describes undernutrition in persons who, for the most part, were living in one town in Germany at one particular time, namely in Wuppertal in August 1946. These subjects had no noteworthy complicating disease; they had consumed little or no alcohol for at least a year; and they were taking a low Calorie diet.

Intestinal flatulence appears early in cirrhosis and is said to be the result of portal venous obstruction. In these patients, however, the flatulence was almost certainly due to the large quantities of vegetables eaten. Signs of bleeding into the skin or from mucous membranes were not found.

Many of the oestrogen effects often seen in liver disease and usually attributed to failure of the hepatic detoxicating mechanism have also been reported in undernutrition. Meienberg and Snell (1946) found erythema of the palms in a few American soldiers who had been prisoners in Japanese hands; Klatskin, Salter and Humm (1947), who studied a group of 300 similar men, found gynecomastia in 36, palmar hyperaemia in 19 and spider naevi in 7; Perakis and Bakalos (1943) reported that they had found cases with spider naevi in Greece. These stigmata were not observed in the Wuppertal group. Clinical enlargement of the liver has been reported by some but not by all workers. Keys, Taylor, Mickelsen and Henschel (1946), who worked with volunteers on a semi-starvation régime, and Leyton (1946), who studied British prisoners of war in Germany, detected no enlargements. However, Bansi (1946), working in Germany, and Meienberg and Snell (1946) found a high percentage of palpable livers, and Klatskin *et al.* (1947) found hepatomegaly in 100 of their 300 cases, and in 50 of these the liver was tender. The fact that the liver was palpable in 9 of the 21 Wuppertal subjects might be adduced as evidence of hepatic change. Large and often fatty livers are found in cirrhosis, but they are usually hard. In this group the liver edge was not tender and was always soft. Moreover, palpability probably bears little relationship to the actual size of the liver (Sherlock and Walshe, 1946). The palpable livers, therefore, were not considered to be a sign that the organ was diseased, and this view was confirmed by inspection of the histological sections, which failed to show any lesion likely to lead to hepatomegaly.

Clinical observations in Wuppertal did not suggest that the subjects had anything wrong with their livers. In hepatic disease, however, clinical impressions are so often fallacious that the more elaborate investigations of structure and function were undertaken.

In experimental animals the liver is readily injured by appropriate experimental diets (György, 1944). The lesions produced fall into two groups. Firstly, acute necrosis, which, if not fatal, is followed by post-necrotic scarring and nodular hyperplasia, and secondly, fatty infiltration, which slowly proceeds to cirrhosis of portal type (Himsworth and Glynn, 1944). In rats the necrotic lesions seem to be caused by too little protein in the diet; they are not influenced by the amounts of carbohydrate and fat. The changes are produced in a matter of weeks (Himsworth and Glynn, 1944).

It is difficult to decide what bearing, if any, the findings of Himsworth and Glynn have on the present investigation. The men in Wuppertal had been living for a year on about 35 g. protein, mostly of vegetable origin, per day, but the hepatic sections that were made failed to reveal any cell necrosis, haemorrhages or post-necrotic scarring. Himsworth and Glynn found that the lesions affected the left lobe of the rat's liver. Our hepatic biopsies were taken from deep in the right lobe, but it is difficult to believe that, even if the left lobe were

mainly affected, the right would show no changes. Since the experimental lesions were patchy, it might be argued that the biopsy was not a fair sample of the liver. It seems unlikely, however, that all 20 biopsies should miss a necrotic or scarred area.

In rats a fatty infiltration, proceeding slowly to diffuse fibrosis, may be produced by giving a diet rich in fat or poor in lipotrophic substances. The fatty change develops in a matter of days, but the diffuse fibrosis does not appear until months later (Himsworth and Glynn, 1944). The undernutrition in Wuppertal had scarcely lasted long enough to have caused fibrotic changes. The intake of lipotrophic compounds (which are mainly in and associated with animal protein) must have been diminished, but the men were on a low-fat diet, and conspicuous fatty changes were never seen in the liver. In starvation the degree to which the liver becomes infiltrated with fat depends upon the quantity of fat available for mobilization from tissue depots (Dible, 1932), which in prolonged undernutrition are so depleted that little fat is available for infiltration. It may be that in the earlier stages of undernutrition hepatic biopsies would show fatty change.

We have failed, therefore, to demonstrate any of the signs of hepatic injury that have been produced so easily in experimental animals by dietetic means.

Apart from the work of Gillman and Gillman (1945) in Africa, which will be discussed later, little information is available about the histology of the liver in human undernutrition. Meienberg and Snell (1946), who obtained one biopsy with a peritoneoscope, found a few slender fibrous bands, which were most noticeable in and about the portal tracts. This was thought to represent an early stage of nutritional cirrhosis. The patient, however, had probably suffered fairly recently from infective hepatitis, and, since a similar histological picture may be seen many months after acute hepatitis (Dible, McMichael and Sherlock, 1943), the changes cannot conclusively be attributed to malnutrition. Since the present findings are at variance with the results of animal experiment, it is a pity that the observations on humans have so far been so few, and more are clearly desirable.

Two main types of pigment were identified in the livers. The brown pigment in the central liver cells was a chromolipoid (haemofuscin), and appeared to be identical with the "wear and tear" pigment normally found in smaller amounts in the central cells. The other pigment was haemosiderin, which was demonstrated mainly in the central and periportal liver cells and in the Küpffer cells. An increased amount of iron in the liver of undernourished persons was observed many years ago by Lubarsch (1921). Gillman and Gillman (1945) who used the aspiration biopsy technique to study the liver in South African natives with pellagra, described the development of a cirrhosis with deposits of haemofuscin and haemosiderin in the liver cells (probably from the mitochondria). There were, however, many differences between the present findings and those described in the South African report. Gillman and Gillman found that a fatty change preceded the deposition of haemosiderin. Later the fat diminished, but in only 17·5 per cent of the adult pellagrins with pigmented livers was fatty infiltration completely absent. If the lesions in Wuppertal were similar to those in South Africa, one would have expected to find considerable fatty infiltration since the haemosiderosis was very slight. As already stated, however, there was no fatty infiltration. In further contrast to the South African work, iron was not demonstrated in the portal tracts, nor were necrosis and disappearance of periportal cells. No portal tract fibrosis was seen nor was the porphyrin-like

fluorescence described when iron is being actively deposited. Sometimes, moreover, the Küpffer cells contained iron when the liver cells did not, a combination of findings not described by the Gillmans.

The findings in this investigation did not resemble those usually described in haemochromatosis (Sheldon, 1935), and the absence of bronzing and of any disturbance in carbohydrate metabolism is particularly to be noted. It is submitted, therefore, that the pigmentation has a simple physiological origin. Although Keys (1946) found a hydraemia in his study of experimental undernutrition in volunteers, a diminished blood volume has been found both in dogs (Weech, Wollstein and Goettsch, 1937; Allison, Seeley, Brown and Ferguson, 1946) and in man (Mollison, 1946; Walters, Rossiter and Lehmann, 1947). Diminished blood volumes and low concentrations of haemoglobin have been found in Wuppertal (*Widdowson*, p. 313 and Table 4, p. 117). During the period of undernutrition there was, therefore, a withdrawal of haemoglobin from the circulation and a liberation of free iron. Moreover, since muscle contains 7 per cent of the total iron in the body (Goodman and Gilman, 1941), the breakdown of myoglobin in the wasting muscles may have provided further free iron. It is probable that the human organism has little or no power of excreting iron once it has been absorbed (McCance and Widdowson, 1937, 1943) and it is suggested, therefore, that the iron found in the liver is to be compared with that found there in pernicious or haemolytic anaemias and represents the excess over present requirements. The liver is certainly one of the main organs concerned with iron storage (Polson, 1928; Bogniard and Whipple, 1932). The histology of the present cases is similar to that described when iron has been released from the breakdown of haemoglobin (Muir and Dunn, 1914–15), but the low or normal concentrations of bilirubin in the serum and the small output of urobilinogen in the faeces indicate that the rate of haemolysis must be slow. Since the haemoglobin in the bloodstream is below normal levels, it is uncertain why the stored iron is not used for the manufacture of new haemoglobin. It has been suggested that the intake of dietary protein may be too low to allow the production of sufficient globin, but there is no concrete proof of this. Accumulations of chromolipoid pigment nearly always accompany the deposition of iron, and may be a preliminary stage in the process. This pigment is not acid fast and does not exhibit yellow fluorescence under the fluorescence microscope. It is probably not identical with the characteristic "ceroid" pigment described by Lillie, Daft and Sebrell (1941) in experimental dietary cirrhosis.

There are very few records of the excretion of urobilinogen in the urine or faeces in undernutrition. In Germany, Bansi (1946) found the excretions to be normal, but neither methods nor results were exactly stated. Leyton (1946) reported that the urine of prisoners of war in a German camp often contained substances which gave a positive reaction with Ehrlich's diazo reagent. Klatskin *et al.* (1947) occasionally found excessive amounts of urobilinogen in the urine of Americans who had been in the hands of the Japanese. The only report available about faecal urobilinogen is that of Watson (1937), who found that subnormal amounts were excreted in inanition and inactivity. In our subjects there was a conspicuous abnormality in urobilinogen excretion, the faecal values being low and the urinary high.

Every care was taken to see that all the faeces were collected and it is thought improbable that any failure in this respect can be the cause of the present findings. Constipation tends to reduce the urobilinogen in the faeces, presumably because more time is available for its absorption from the intestine (Watson,

1937; Maclagan, 1946). Watson states that low excretion of urobilinogen due to low faecal weight can be expected if the collection for four days is less than 250 g. In the present tests, the mean faecal weights for each of the three days were normal, and the average weight of the total three-day collection was 311 g. The faecal weights, however, may have been increased by the high vegetable residues and may not be as "normal" as they appear for the majority of our subjects had no bowel movement on one of the three days and a few had none on two of the three days.

Although association of increased urinary urobilinogen with hepatic haemosiderosis suggests excessive haemolysis, the normal serum bilirubin concentration and the low faecal urobilinogen excretion do not support this; moreover, the anaemia recorded was very mild. The increased urinary urobilinogen might reflect hepatic damage. This, if present, must have been minimal and was not shown histologically or in the results of bromsulphthalein and other tests of hepatic function. It is to be expected that, although the iron of the liberated haemoglobin is retained, the porphyrin complex will be excreted into the intestine. The urobilinogen reabsorbed may not be utilized for new haemoglobin production, and is, therefore, excreted into the urine. If this is correct, a higher faecal urobilinogen concentration would have been anticipated; the low values recorded may, however, be due to the factors already discussed.

Meienberg and Snell (1946) used the bromsulphthalein test as one of the principal criteria for detecting hepatic dysfunction, and in their series of 50 liberated prisoners of war they found slight dye retention in 13 and moderate in 11; the icteric index was a little raised in 17. Most of their cases, however, had recently suffered from infective hepatitis. Klatskin *et al.* (1947), who studied a similar group, found abnormalities in the total and in the proportion of direct and indirect serum bilirubin. Mollison (1946) found that the serum of prisoners in the Belsen concentration camp was not icteric. In this series the total serum bilirubin and the bromsulphthalein tests were always normal. The findings have already been discussed in relation to the hepatic pigment changes and the urobilinogen excretion.

We can find no reference to the quantitative estimation of liver glycogen in human undernutrition. In rats, starvation for 48 hours causes a diminution of glycogen (Lawrence and McCance, 1931). In dogs, the glycogen varies in a general way with the amount of carbohydrate in the diet; there is a decrease with fasting or with a high-fat or a protein diet (Bollman and Mann, 1936). Elman, Smith and Sachar (1943) showed that in dogs a 54-hour fast produced an extremely low hepatic glycogen, assessed either chemically or histologically. The percentage of glycogen in the small hepatic biopsies is probably indicative of the amount in the liver as a whole, and the amount in different lobes is sufficiently uniform for a specimen from one lobe to be representative of the whole (Schöndorff, 1903; Grube, 1905; MacIntyre, Pedersen and Maddock, 1941). There must, of course, be some sampling error, but for a sufficiently large series the comparative error must be very small. In the Wuppertal subjects the glycogen was quantitatively normal. This may have been due to the length of time the men had been on the defective diet, since there was probably time for adaptation by lowering the metabolic rate. The low values, moreover, were found in animals after a long fast, whereas our biopsies were taken after a fast of only 12 hours.

It is very difficult to make any quantitative estimate of glycogen by histochemical methods. The stainable polysaccharide is unequally distributed, not

only from lobule to lobule, but within the lobule, and even within single cells. Grafflin, Marble and Smith (1941) found a rough correlation between the histochemical and microchemical methods, but individual discrepancies were numerous. We encountered similar differences, and agree with Grafflin *et al.* that histochemical estimation is unreliable when a quantitative assessment of glycogen is required. Recently Deane, Nesbett and Hastings (1947) have improved the technique for fixing hepatic glycogen, and have measured the optical density of suitably stained sections with a photometer. The results were stated to compare favourably with those obtained by chemical methods, but sections taken by biopsy are not large enough to be treated satisfactorily by this method. Histologically, glycogenic infiltration of the nuclei was the only observed change in glycogen distribution and was seen in 40 per cent of the subjects. Chipps and Duff (1942) reported that they had found glycogen in the nuclei in 39 per cent of 315 routine autopsies but that they were unable to discover any constant factor, except possibly diabetes, to account for the infiltration. We have also found glycogen in the liver-cell nuclei at autopsies at the British Postgraduate Medical School and it is doubtful whether the finding has any pathological significance in the biopsy sections obtained in Wuppertal.

The liver is mainly responsible for the maintenance of a normal blood glucose (Soskin, 1941), but extremely severe liver damage is required to produce hypoglycaemia, and it is not surprising, therefore, that normal values only have been found in the present series. Robinson, Shelton and Smith (1941) found that undernutrition in man was associated with a glucose tolerance test of diabetic type. This could not be confirmed in the present series. It is the ratio of carbohydrate to fat in the metabolic mill that determines the shape of the glucose tolerance curve (Himsworth, 1935,) and although the Wuppertal patients were short of carbohydrate, they were even shorter of fat. The findings are in agreement with those of Morgulis (1923) that a low Calorie diet has little effect on the utilization of carbohydrate.

Berridge (p. 97) has described radiological appearances in the small intestine resembling those to be seen in sprue. It is interesting, therefore, that the sugar tolerance curves were not flat as they often are in this disease.

The administration of adrenaline to man reduces the amount of glycogen found in the liver (Hildes, Sherlock and Walshe, 1949), and the rise in blood sugar produced by adrenaline is at least partly due to the mobilization of this glycogen. Bansi (1946), working in Hamburg, reported a poor blood sugar response to adrenaline in undernourished persons, but this was not confirmed at Wuppertal. Not only was the hepatic glycogen quantitatively normal, but it was freely mobilized under the stimulus of adrenaline.

The administration of insulin tests two functions. The rate of the initial fall of the blood sugar measures the rate at which glucose is taken up by the tissues under the influence of insulin and the rise in the blood sugar after the insulin-induced hypoglycaemia measures the speed of mobilization of the glycogen, probably from the liver (Fraser *et al.*, 1941). Persistent hypoglycaemia has been reported in some cases of anorexia and also in malnutrition (Fraser and Smith, 1941). The normal results in our subjects show that glucose was readily removed from the blood and also that glycogen was freely mobilized.

Chronic undernutrition induces structural and functional alterations in the hypophysis, which result in decreased pituitary activity (Stephens, 1941). Some of the clinical features in our patients have suggested hypopituitarism, but the insulin tolerance tests were normal. Chambers (1938) is doubtful whether

undernutrition *per se* is responsible for any gross interference with the mechanism for handling carbohydrate in the body, and the present findings are in agreement with this.

In undernutrition the level of alkaline phosphatase in the serum may, theoretically, be altered in at least three different ways: a low Calorie diet may depress it, hepatic damage produced by a low protein diet may raise it, and so may famine osteomalacia. These changes will now be considered. In the experimental animal, fasting reduces the activity of the serum phosphatase (Freeman and Farmer, 1935; Weil and Russell, 1940), and a similar result has been produced in rats by long periods of undernutrition (Bodansky and Jaffe, 1931). The phosphatase is restored to normal by giving carbohydrate, which may act by stimulating the intestinal mucosa to produce more phosphatase (Bodansky, 1934). The high proportion of carbohydrate in the diets at Wuppertal may have helped to maintain the serum phosphatase within normal limits. Animals whose livers have been damaged by a protein-deficient diet have high phosphatase activity in their sera (Hough and Freeman, 1942). This increase is believed to be a sensitive indication of hepatic dysfunction (Drill and Ivy, 1944), and the normality of the serum phosphatases in the undernourished people in Wuppertal is therefore further evidence that their livers were functionally and structurally sound. Famine victims in Holland who suffered from osteomalacia usually had a raised phosphatase (Pompen, Chapelle, Groen and Mercx, 1946). However, of the 24 patients described, 22 were women, whereas our patients were adult males, and they presented no radiological evidence of osteomalacia (*Berridge and Prior* p. 289). In keeping with this, their sera, as already stated, contained normal amounts of phosphatase.

In rats or mice starvation and protein depletion alter the amounts of phosphatase normally found in the liver cells. The atrophic liver cells of starvation have been stated to show an increase in cytoplasmic alkaline phosphatase, whereas the fat-laden cells of protein deficiency show a decrease (Wachstein, 1945). In man hepatic damage due to carbon tetrachloride poisoning or acute hepatitis, even if histologically minimal, produces a conspicuous change in the amount and distribution of hepatic alkaline phosphatase (Sherlock and Walshe, 1947). In the biopsies taken in Wuppertal the alkaline phosphatase in the liver cells was histochemically and microchemically normal, providing further evidence that the livers were healthy.

The colloidal gold precipitation test probably depends on the gamma globulins in the serum. Raynaud and Laroche (1943) and many others have found that in human undernutrition the serum globulins, as a whole, may be reduced. The present investigations have confirmed this. The gamma globulins in the serum may show little relation to the total globulin, but they also may be low in human undernutrition (Krebs, 1946; *Kekwick*, p. 207). Since a positive reaction with colloidal gold is probably the result of high rather than low gamma globulins in the serum, the results obtained at Wuppertal are easily explained. No reason can be given for the two positive reactions.

Starvation of short duration causes a rise in the total cholesterol (Shope, 1927) in the serum, but more prolonged undernutrition usually results in a fall (Entenman, Changus, Gibbs and Chaikoff, 1940). This was noticed in Germany after the first world war (Rosenthal and Patrzek, 1919) and Man and Gildea (1936) found that on the whole the serum cholesterol varied with the state of nutrition. In normal man the total cholesterol in the serum and the esterified cholesterol both fluctuate widely, but the ratio of the two is much more constant

(Greene, Hotz and Leahy, 1940). There are few reports on the changes produced by undernutrition. Kartin, Man, Winkler and Peters (1944) found that short periods of fasting produced a rise in both free and esterified cholesterol. The increase of free cholesterol was comparatively large, much more so than that of the ester. Hodges, Sperry and Anderson (1943) found a subnormal percentage of the total cholesterol present as the ester in undernourished children. There was a good deal of individual variation. The present results agree with those of Hodges et *al.* (1943). The fall in ester cholesterol is of uncertain origin. Low levels are found in liver disease (Man, Kartin, Durlacher and Peters, 1945), but the other findings exclude this. From the lowered basal metabolic rates that were found in many of the Wuppertal subjects one might have expected the serum cholesterol to be high, for diminished thyroid function, whether primary or secondary to hypopituitarism, is often associated with high levels of cholesterol in the serum.

If the kidneys are healthy, a normal result for the hippuric acid test depends both on the production of adequate amounts of glycine and also on the conjugation of this glycine with the benzoic acid. The low results in liver disease are probably due to failure of the liver to produce the glycine (Quick, 1931; Vaccaro, 1935), but a conjugation defect has been suggested (Probstein and Londe, 1942). The normal subject is able to produce enough glycine to eliminate 1·33–1·91 g. of hippuric acid per hour (Quick, 1932), an amount well above that normally required for the hippuric acid test. Some of the glycine is derived from glycine already present in the tissues, but some of it is synthesized (Quick, 1931). If the previous diet has been rich in protein, more benzoic acid may be converted to hippuric acid (Lewinski, 1908). It is perhaps surprising that the Wuppertal subjects on low-protein diets and with low serum proteins should have given normal results for the hippuric acid test. It must therefore be assumed that glycine (the simplest of the amino-acids) can easily be made available even in people who are seriously undernourished.

SUMMARY

1. Hepatic structure and function were studied in 18 civilian citizens of Wuppertal and in 3 prisoners in Siegburg gaol in August 1946. They were all undernourished and had lost 2–55 kg. in weight.

2. Clinical history and examination did not indicate hepatic dysfunction.

3. The hepatic histology was generally normal. There was no necrosis, cirrhosis or fatty change in any of the sections.

4. The liver cells sometimes contained considerable amounts of iron and chromolipoid pigment. These changes are thought to have followed a reduction in the amount of haemoglobin and myoglobin.

5. The output of urobilinogen in the urine was often greater than normal and in the faeces less than normal. The total bilirubin in the serum was within normal limits and the bromsulphthalein tests were normal.

6. The hepatic glycogen, the fasting blood sugar, the oral glucose tolerance and the adrenaline and insulin sensitivity tests were normal.

7. The hepatic alkaline phosphatase in the liver cells was normal in distribution and amount. The alkaline phosphatase in the serum was also within normal limits.

8. The serum colloidal gold reaction was usually negative.

9. The concentration of total cholesterol in the serum was often low. The percentage of the total cholesterol in ester form was also low.

10. The intravenous hippuric acid synthesis test gave normal results.

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VI. ENLARGEMENT OF THE PAROTID GLANDS

by R. A. McCance, R. F. A. Dean and A. M. Barrett

PREVIOUS OBSERVATIONS

In 1922 Erlich reported that in 1916–17 large numbers of Polish children of both sexes under 13 had an enlargement of their parotid glands. By 1918 the percentage affected was decreasing, and with the return of plenty the syndrome disappeared. No histological examinations were made, but the swelling was attributed to hypertrophy. In 1937 chronic enlargements of the parotid and sometimes of the submaxillary glands were reported to be not uncommon among poor agricultural workers in Egypt; women were rarely affected. Many of the series of men with large parotids were found to have pellagra, some had diabetes and all were probably undernourished. Post-mortem and biopsy material showed that the swellings were due to a non-inflammatory hypertrophy (Kenawy, 1937). Kekwick (1949) has informed us that chronic enlargement of the parotid glands is well known in Kenya, and Gillman, Gilbert and Gillman (1947) stated that it was comparatively common among malnourished Africans. Gigon (1938) described an enlargement of the parotid glands in an alcoholic, and Kanther (1948) noted swellings of the parotids in some of the men in camps for prisoners of war in Russia; some of the men also had enlargement of the breasts (Trautman and Kanther, 1947). In all these cases the swellings appeared while the people were undernourished and before there was any suggestion of improvement in their circumstances.

Other investigators have also produced evidence that the size of the parotid glands may be affected by the plane of nutrition, but it is by no means certain that the syndrome they describe is the same as the one just outlined. Thus Sprinzels (1912) gave a clear description of hypertrophy of the parotid glands associated with great fatness in men. No histological examinations were made, but Sprinzels pointed out that palpable breasts were often associated with the enlarged parotids. Eigler and Boenninghaus (1948) described parotid enlargement in Germans who were putting on weight after their repatriation from Russia. They reported that the glandular swellings were soft, and the overlying skin normal. There was nothing to suggest inflammation or oedema of the glands or the surrounding parts. The swellings were not painful and did not increase in size during or after meals. The two sides were not invariably symmetrical. Bansi (1949) considered that these enlarged parotid glands, commonly seen in men repatriated from Russia, formed part of a much more general syndrome, affecting both sexes, which he described under various names such as "die lipophile Form der Dystrophie", "Mangelfettsucht", "Paradoxe Fettsucht", etc. Stevenson (1949) observed outbreaks of parotid enlargement among Russians who had been prisoners of war in German hands during the second world war. The men, who had recently been released, were eating enormous quantities of bread and other food at the time and were gaining weight. Kekwick (1949) has stated that men admitted to Kisumu gaol with advanced undernutrition commonly developed swollen glands as their weight and health improved on the prison diet. Flaum (1932) reported a very similar syndrome in diabetics or pre-diabetics who were getting fat, and Davies (1948a) that swollen parotids were one of the first signs of recovery in kwashiorkor.

The gynecomasty which has already been mentioned has also been described without parotid enlargement in prisoners of war who had been in Japanese

hands (Hibbs, 1947; Klatskin, Salter and Humm, 1947; Salter, Klatskin and Humm, 1947). The men developed these enlarged and often tender breasts before or sometimes after their repatriation, but characteristically the enlargement was preceded by a considerable gain in weight. This gynecomasty has been explained by supposing that the undernutrition injured the liver cells in such a way that they failed to destroy oestrogens (Davies, 1948b). Many of the patients seen by Klatskin *et al.* (1947) had enlarged livers or a history of hepatitis, but Salter *et al.* (1947) found no evidence that they were under the influence of an excess of oestrogens. An excess of these hormones can hardly explain enlargement of salivary glands where there is no development of the breasts, but the liver may yet turn out to be involved in the parotid enlargements, for Lang (1929) described a post-mortem in which true parenchymatous hypertrophy of parotids was associated with atrophic cirrhosis of the liver.

The parotid enlargement has been attributed to interstitial oedema (Eigler and Boenninghaus, 1948), to fatty infiltration (Bansi, 1949), to parenchymatous hypertrophy (Kenawy, 1937; Gigon, 1938) or to "work" hypertrophy (Kanther, 1948). Luckner and Scriba (1948) found only atrophy of the salivary glands in their undernourished rats in 1938, but suggested that the clinical enlargement in repatriated prisoners of war was due to oedema or to glandular regeneration preceding the regeneration of the neighbouring parts. Gillman *et al.* (1947) attributed the enlarged glands to an increase in the size of individual cells, but they also reported atrophy of the salivary glands in undernourished Bantus, with a terminal stage histologically resembling cystic fibrosis of the pancreas. In considering the differential diagnosis of parotid swellings, Weber and Schlüter (1937) did not discuss any of the syndromes just described.

PRESENT OBSERVATIONS

Enlarged parotid glands were a common sight in 1947–8 in German men who had recently been repatriated from Russia. These men were generally thin and underweight on their return to Germany, and their faces also looked thin. They immediately began to put on weight very rapidly. Their cheeks became fatter, but at the same time their parotids began to swell, and this made their ears stick out in a very characteristic way. By the end of two or three weeks the swelling was usually very obvious. The enlargement of the parotids always followed the return to a generous diet, and it usually accompanied the general obesity. The nipples were not enlarged or pigmented and there was no evidence of gynecomasty. It is true there was often considerable deposition of fat over the pectoralis muscle and around the nipple, but this could be said of almost every other part of the body. The glands slowly subsided as the men regained metabolic equilibrium. Undernourished civilians never had enlarged parotid glands, nor did the civilian prisoners at Siegburg gaol.

The swellings were soft but not cystic, usually but not invariably symmetrical, and painless. There was no evidence of inflammation in or around the glands. The ducts were not obstructed and the size of the swelling was not affected by the taking of food. The submaxillary glands were usually quite normal in size, but occasionally one or both were also enlarged. Plate LI is a full-face photograph of a man with a fat face and swollen parotid glands. Plate LII shows the profile of a man whose face was not so fat, but whose parotid gland is clearly outlined by the shadows it throws on his face.

Glandular tissue was obtained *post mortem* from a man who had very swollen

parotids during life and who had died of acute infective endocarditis after a short illness of eight or nine days. The material was preserved in formol saline and brought to Cambridge for examination.

Paraffin sections were stained by Ehrlich's haematoxylin and eosin, and by McFarlane's picro-Mallory method, and they were compared with sections of 14 apparently normal parotids obtained at routine necropsies in England. No definite histological abnormality was observed in the sections of the enlarged parotid; there was no trace of any inflammatory cellular infiltration or fibrosis, and the amount of adipose tissue was certainly within normal limits, although the individual fat cells were rather large (Plate LIIIa, b). It therefore seemed that the increase in the size of the gland must be due either to an increase in the size of the individual acini, or to an increase in their number, or to both. In order to get some idea whether or not there had been any increase in size, 10 representative acini (each from a different field) from 12 normal parotid glands were drawn at a magnification $\times 625$, using a projection apparatus. The longest and shortest diameters of each acinus were then measured and averaged, and the values for the mean diameters of the 10 representative acini were averaged. The same procedure was carried out 10 times on the section of the enlarged parotid, so that 10 separate estimates of the diameters of the acini of this gland were obtained. Accurate determination of the mean size, based upon the measurement of a large number of unselected acini, would have been preferable, but the acini varied so much in size and shape, and were cut in so many different planes, that this was considered to be impracticable.

The mean diameters of the acini of the 12 apparently normal glands were 27·5, 26·3, 31·9 32·1, 28·0, 24·3, 33·9, 31·9, 30·6, 35·4, 28·2 and 28·5 μ (average 29·9 μ), and of the enlarged parotid gland 35·9, 38·5, 36·7, 38·5, 36·4, 39·6, 35·2, 36·8, 39·7 and 35·6 μ (average 37·3 μ).

Although these results cannot be regarded as conclusive, they suggest that the enlargement of the parotid may have been due at least in part to an enlargement of its individual acini. In this connexion it should be borne in mind that the estimates are of diameters and that there must have been a relatively greater difference in the areas of the cross-sections and still more in the volumes of the acini. No evidence of cell multiplication was found; no mitoses were observed, and the abnormal parotid did not appear to contain more nuclei per acinus than the controls. In the normal parotids the cells of the acini had often shrunk away from the basement membrane, but in the enlarged parotid they had not done so. In the normal parotids the secretion granules were often confined to the parts of the cells next to the lumen, leaving the cytoplasm at the base of the cells free from granules and with the appearance of ground glass, whereas in the enlarged parotid the whole of the cytoplasm contained granules or fine vacuoles probably derived from granules. In the acini of the enlarged parotid the nuclei appeared to be compressed on to the base of the cells, close to the basement membrane. These differences (Plate LIVa,b) indicate greater functional activity of the enlarged parotid, but it would be unwise to attribute much importance to such differences in necropsy specimens.

The clinical findings in Wuppertal agreed with those of Eigler and Boenninghaus (1948), who had similar material under observation, but the histological evidence shows that the swellings were due to hypertrophy of normal gland tissue and not to fatty infiltration as suggested by Bansi (1949). The reason for this hypertrophy is not clear, and speculation is made more difficult by the fact that the earliest stages were seldom, if ever, seen in Wuppertal. It was

therefore impossible to relate the initial signs of hypertrophy to the time at which the men first obtained a generous diet. The impression gained was that these swellings were part of the response to overfeeding after a prolonged period of undernutrition. If this is true the enlargements may be regarded as a work hypertrophy, perhaps as a sign of recovery, and the syndrome may be similar to the one described by Sprinzels in 1912, by Flaum (1932), by Davies (1948a) or by Stevenson (1949) and Kekwick (1949), but it cannot be quite the same as the syndromes written up by Erlich (1922), Kenawy (1937), Gigon (1938), Trautmann and Kanther (1947) and Kanther (1948), in all of which the swellings were noted while the subjects were seriously undernourished.

It remains to explain why the syndrome was not noticed among the civilian population or at Siegburg gaol. The supply of food for the civilian population improved very gradually over a period of two or three years and never became excessive. Hence there was plenty of time for adjustment to take place, and there was no sustained overactivity of the digestive glands. The repatriated men came back from a prolonged period of undernutrition during which their salivary glands had probably atrophied *pari passu* with the rest of the body. They at once began to eat enormous quantities of food—mostly a hard dark bread that required much mastication—and the result was hypertrophy of the parotid glands. The 19 undernourished civilians who ate a diet providing 6,000 Calories per day for eight weeks (*Widdowson*, p. 313) did not develop enlarged parotids, but the repatriated prisoners of war studied by *Widdowson and Thrussell* (p. 296) did. The diet of the latter provided 7,000 Calories a day. The undernourished civilians, however, ate only 590 g. of bread per man per day, whereas the repatriated prisoners of war ate 1,260 g.

The rate at which the glands hypertrophied in relation to the general deposition of muscle and fat (Luckner and Scriba, 1948) would go far towards explaining most of the clinical findings, and might even explain some of the observations made while the men were still in camps.

The parotid glands of some animals contain a very active pseudocholinesterase (Mendel and Rudney, 1943; Augustinsson, 1948), and the activity of this enzyme in the serum rose to levels above the normal in many of the obese repatriated prisoners with swollen parotids (*Hutchinson, McCance and Widdowson*, p. 216). The association, however, would appear to have been fortuitous, for only traces of cholinesterase could be extracted *post mortem* from human parotids by methods that gave very active preparations from the parotids of the pig (Hutchinson, 1949).

SUMMARY

1. Enlarged parotid glands were common in German men who were rapidly gaining weight after being repatriated from camps for prisoners of war in Russia.

2. The swellings were not tender or inflamed, and a post-mortem examination of one gland showed that the tissue was essentially normal.

3. The men with the swollen parotids did not have enlarged breasts.

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VII. NEUROMUSCULAR SYSTEM: TENDON REFLEXES AND GALVANIC RESPONSES

by R. A. McCance and R. F. A. Dean

Semi-starvation and malnutrition in the Far East and in many other parts of the world have usually been associated with widespread lesions of the peripheral and central nervous systems. Beriberi, with its characteristic peripheral neuritis, was one of the first diseases that was recognized to be due to a nutritional deficiency, and pellagra is well known to give rise to neurological lesions of the cord and brain. During the second world war prisoners in the hands of Japanese suffered from a number of neurological abnormalities. Central and peripheral neuritis, painful feet, captivity amblyopia, central scotomata and night blindness were all common and have been described by many people (Spillane, 1945; Bennet, Smith, McGregor, Burgess, Cruickshank and Williams, 1946; Burgess, 1946; Clarke and Sneddon, 1946; Cruickshank, 1946; Dansey-Browning and Rich, 1946; Durran, 1946; Garland, 1946; Graves, 1946; Goldsmith, 1946; Harrison, 1946; Hibbs, 1946; Hobbs and Forbes, 1946; Jackson, 1946; Kuilman, 1946; van Manen, 1946; Mitchell and Black, 1946; Page, 1946; Price, 1946; Rich, 1946; Simpson, 1946; Stening, 1946; Williamson, 1946; Brain, 1947). A summary of this literature has been given by Walters, Rossiter and Lehmann (1947a, b) and their articles should be consulted for further references. Spillane and Scott (1945) described similar neurological findings in German prisoners of war in the Middle East. A number of these papers bear the stamp of hurried composition, and there is no doubt that many of the signs and symptoms described therein as new had previously been observed in Africa, India, and possibly also in China (Gopalan, 1946). Stannus (1911–12, 1913–14), for example, clearly described hyperkeratosis, painful or burning feet and central scotomata in Nyasaland before the war of 1914–18, and an interesting article by Moore (1946) should be consulted for further historical details.

The undernutrition that was prevalent in Central Europe during and after the first world war was not characterized by gross neuromuscular disturbances. Jansen (1918) found none; Schittenhelm and Schlecht (1918, 1919) reported that many of their patients complained of night blindness, and had sluggish knee jerks and nerve trunks which were occasionally sensitive to pressure. Careful and complete examinations of the nervous systems, however, failed to reveal anything abnormal. The second world war has again been responsible for much malnutrition in Europe, and many reports of the findings have been published. Neurological disorders have been rare or absent (Leyton, 1946), but polyneuritis has been diagnosed in Holland (Lohr, 1947) and in some of the German concentration camps (Rosencher, 1946). A very short note of an outbreak in France, which was thought to be beriberi or at any rate to respond to vitamin B_1, was published by Sivadon (1941). Some of the German, Dutch and Belgian observers have also claimed that they have found neurological and other evidences of aneurin deficiencies. Thus Heilmeyer (1946), writing of his experiences in Jena and Wuppertal, has stated:

Recht häufig kommen jetzt auch B_1-Mangel-Neuritiden zur Beobachtung, die sich hauptsächlich an den unteren Extremitäten manifestieren. Noch bevor objektive Symptome nachweisbar sind, kommt es zu Störungen der Gehfähigkeit. Die Kranken klagen über Schwäche in den Beinen; ihr Gang wird unsicher, oft taumelnd. Nicht selten bestehen ausgesprochene Gleichgewichtsstörungen. Das Romberg'sche Phänomen kann stark positiv

sein. Bei der Untersuchung fällt der breitbeinige, wackelige, ataktische Gang auf. In dem ersten Stadium der Erkrankung sind die Reflexe manchmal gesteigert. Meist kommt es aber zu Reflexabschwächung oder zu völligem Reflexausfall, sowohl an den unteren wie auch an den oberen Extremitäten. In schweren Fällen kommt es zu deutlicher Atrophie der befallenen Muskeln.

Auch die Sensibilität ist leicht gestört. Die neurologische Untersuchung deckt Ausfälle für alle Qualitäten auf. Manchmal ist die Kalt-Warm-Empfindung stärker gestört als die Berührungsempfindung. Subjektiv klagen die Kranken frühzeitig über ein Gefühl von Taubheit und Kribbeln, besonders in den Zehen. Stärkere Schmerzen im befallenen Gebiet sind gewöhnlich nicht vorhanden.

These findings have been echoed by other Germans writing in their new medical press, but it is difficult to see why there should have been any lack of B vitamins in the German diets, and Strauzenberg (1946) was certainly not justified in saying that the diet was one likely to lead to hypovitaminosis B. Similar claims were, however, made by one Belgian investigator during the war (Simonart, 1942, 1945), and Devis and Simonart (1942) have attempted to substantiate their neurological findings by claiming to have detected chemical evidences of B_1 deficiencies. Subnormal excretions of the vitamin and raised blood pyruvates were reported, but the former finding was not in line with the work of Crismer (1941a, b) and no signs of aneurin deficiencies have been found in Germany by the British survey teams. Keys, Taylor, Mickelsen, Henschel and Brozek (1946) met with no neuromuscular disturbances other than sluggish reflexes among the 34 volunteers who lived for six months on a diet of 1,400 Calories a day. These diets were made up to resemble those likely to be obtainable in Europe, and there was no evidence that they led to any deficiencies of the vitamin B complex.

Soon after the Unit was established, it was noticed that many of the persons applying for extra rations had very exaggerated knee jerks, and more detailed clinical examination suggested that other reflexes might be affected. This was unexpected, but similar observations have been made before, and the literature will be discussed after the syndrome has been described.

THE CLINICAL SYNDROME

Exaggerated reflexes were observed in adults, young and old and of either sex. Children were not found to be affected. The frequency of the syndrome may be judged from the fact that abnormally active reflexes were found in 123 out of 372 out-patients seen during the months of September, October and November, 1946. A light tap with the percussion finger often elicited a brisk contraction of the extensor muscles of the leg, and the arm jerks were equally remarkable. The responses tended to be not only brisk but diffuse. In the case of the knee jerk, for instance, crossed responses were often detected. When the supinator reflex was elicited, flexion of both the arm and the fingers might be observed. In a proportion of cases the true reflex was accompanied by a secondary jump, which might involve a large part of the skeletal musculature. It was not always easy to be sure whether the widespread response that was obtained was due to an exaggeration of the reflex or to a semi-voluntary jump. In rare cases the muscular contraction was accompanied by a slight gasp or, occasionally, by an exclamation. The abdominal reflexes were sometimes normal even when the tendon reflexes were not, but on occasions the abdominal reflexes in elderly men were as active as those of a baby. Some very active cremasteric reflexes were seen. Extraordinary displays of reflexes could be elicited by striking the tendons or bellies of the muscles attached to the scapula, and on several occasions a spurious Chvostek sign was elicited by tapping one

of the facial muscles. It was found, moreover, that the briskness of the reflexes varied from day to day. They tended to become more normal with rest, and sometimes a man who had been an exhibition case in the out-patient department or on admission would put up rather a disappointing display after four or five days in hospital.

Eight patients with highly abnormal reflexes were questioned about the history of their troubles and subjected to a detailed neurological examination. Each man was examined for his aural acuity; the shape of his pupils and their reaction to light and accommodation; his eye movements, including nystagmus; his fundi and his visual fields; his facial movements, particularly those of his forehead and mouth; the direction in which his tongue protruded, the presence or absence of wasting or tremor in it and the characteristics of its surface; the movements of his palate; his superficial facial sensation; and the presence of a true or a false Chvostek sign, of a masseter and of a jaw jerk. His head and shoulder movements were inspected, and his upper limbs were scrutinized for localized wasting and for fasciculation. An attempt was made to elicit Trousseau's sign and he was tested bilaterally for dysdiadokokinesis, position sense, past pointing, tone, muscular strength and intention tremor. His lower limbs were examined in the same way for wasting, fasciculation, power, tone, clonus and position sense. He was asked to pass the heel of each leg along the tibia of the other. Romberg's and Babinski's tests were applied, and his ability to walk heel to toe forwards and backwards with and without visual assistance was tested. His upper and lower limbs were examined for vibration sense and for the reaction of the skin to heat and cold, to touch with wool and with sharp and blunt instruments. His skin was inspected for trophic changes. These tests revealed no certain abnormalities. Cerebrospinal fluid was withdrawn from each person and the results of the tests made upon it are given in Table 1. It will be seen that these tests, taken as a whole, provided no clue to the cause of the exaggerated reflexes, but they did, at any rate, help to exclude most of the well-recognized neurological diseases.

A study of the literature made it clear that the syndrome which was so characteristic of the out-patients at the Barmen clinic had probably been encountered before. Thus Gounelle, Raoul and Marche (1941) had described exaggerated knee and ankle jerks without any other neurological abnormalities in a group of people who had been living for some time on a diet providing about 1,500 Calories per day, and Burger, Sandstead and Drummond (1945) mentioned that just after the liberation of Holland the reflexes of some of the elderly people were conspicuously overactive, and it was implied that no other neurological abnormalities were present except possibly minor paraesthesiae. Cruickshank (1946), Clarke and Sneddon (1946), Harrison (1946), and Simpson (1946) may have had the same syndrome under observation. Others have described exaggerated knee jerks as part of a widespread neuropathic syndrome. Thus Spillane and Scott (1945) described severe ataxia coupled with a positive Romberg test and greatly exaggerated knee and ankle jerks as one phase in the development of their "ocular neuropathy". They stated that the plantar responses were never extensor and that the abdominal and cremasteric reflexes remained brisk, so that, but for the Romberg test and the ocular signs, the findings were not unlike the present ones. Gopalan (1946), in describing a burning foot syndrome in Indian natives, mentioned that knee jerks were brisk and that there was excessive sweating of the affected parts. Price (1946) described cases of spastic paraplegia with exaggerated reflexes accompanied by an extensor

TABLE 1

Serum and cerebrospinal fluid chemistry in patients with brisk reflexes

Subject No.	Serum		Cerebrospinal fluid								
	Ca (mg./100 c.c.)	Mg (mg./100 c.c.)	Pressure (mm. H_2O)	Queckenstedt	No. of cells in 3 fields	Cl (mg./100 c.c.)	Protein (mg./100 c.c.)	Panda	Nonne-Apelt	W.R.	Lange
B 84	9·45	2·58	100	pos.	2	477	25	neg.	neg.	neg.	—
B 98	8·80	2·32	140	pos.	10	460	—	neg.	neg.	neg.	—
B 105	10·6	—	80	pos.	2	—	25	neg.	neg.	neg.	0 × 10
B 107	9·05	—	90	pos.	4	—	25	neg.	neg.	neg.	0 × 10
B 112	8·8	—	110	pos.	21	456	30	neg.	neg.	neg.	0 × 10
B 113	9·8	—	145	pos.	2	453	25	neg.	neg.	neg.	0 × 10
B 116	10·2	—	95	pos.	2	505	—	neg.	neg.	neg.	—
B 118	8·8	—	45	pos.	1	485	30	neg.	neg.	neg.	2221110000

plantar response in prisoners of war from the Far East, and considered the diagnosis of lathyrism. Gopalan found Marmite and especially calcium pantothenate to be effective in treating the sensory changes, but did not say whether the reflexes were simultaneously subdued. Clarke and Sneddon (1946) could not establish that any dietary deficiency accounted for the neuropathy, although associated skin changes were healed with vitamin treatment, and, in view of the mode of development of the neurological signs, they postulated a toxic or anti-vitamin agent.

It was decided to undertake a short therapeutic trial, to discover if aneurin affected reflex activity. Ten patients with brisk reflexes and with various amounts of oedema were given 25 mg. aneurin (Betaxin, kindly supplied by the makers, Bayer-Fabrik, Elberfeld) each day for seven days. Seven of the patients received it by injection and the rest in the form of pills. Four similar patients were at the same time given dummy pills. At the beginning and end of the trial the reflex activity was assessed by an examiner who did not know which patients had been given the aneurin. No certain effect of the vitamin could be detected. The reflexes remained unchanged, and, although the group receiving aneurin lost a small amount of weight, the group receiving the dummy pills lost more. It was therefore concluded that these patients had derived no benefit from treatment with these amounts of aneurin.

GALVANIC RESPONSES

The hospital at Barmen was equipped with an apparatus for measuring the responses of the neuromuscular system to galvanic stimulation, and one of the German doctors, who had had some experience of the technique, undertook to measure the electrical responses of a series of normal British and undernourished German persons. He also measured the responses in a few of the German hospital staff and in the group of 19 undernourished people before and after they had been given an excellent diet for two months (*Widdowson*, p. 313). Before being placed upon the skin the electrodes were immersed in water, not, as is more usual in England, in a solution of zinc sulphate, but this point had previously been investigated at Barmen and the two fluids had been found to give the same results.

The minimum opening and closing currents required to produce visible muscular responses were measured in the usual way, and the results obtained in 1946 indicated that undernutrition lowered the minimum galvanic current required to excite the bellies of the biceps and gastrocnemius muscles, and the peroneal and ulnar nerves. The differences between the responses of the controls and of the undernourished people were statistically significant and the changes brought about by a good diet were also statistically significant. The reason for these results was not at all clear. The only reference to a similar phenomenon in the literature was a curious sentence in an otherwise uninspired article by Schäfer (1946): "Die oft festgestellte erhöhte mechanische und elektrische Erregbarkeit der Nerven und der Muskulatur (Hungertetanie) deutet vielleicht auf eine Störung der Epettelkörperchenfunktion". It might have been expected, moreover, that the abnormally brisk reflexes would have been correlated with an increased excitability to the galvanic current but, in fact, an attempt to correlate the two variables ended in finding insignificant coefficients.

In 1947, therefore, Newman and Tomson re-investigated the whole matter. They used the same apparatus and re-tested some of the previous controls. The reflexes of the Germans were not so exaggerated at this time and the German

civilians were not so undernourished, but Newman and Tomson tested the leanest they could find together with many very undernourished young men who had recently returned from Russian prison camps. In all, 62 Germans and 29 young British subjects were investigated. Newman and Tomson were unable to confirm the results of the year before, but it was impossible to point out any obvious flaw in the old technique or to discover what change, if any, had taken place in the experimental conditions. It seems justifiable, therefore, to place the findings of 1946 on record, although it must be pointed out that, even if the observations then made were correct and reproducible, they would not go far towards explaining the exaggerated reflexes. An alternative explanation has been advanced by *Davis* (p. 147).

SUMMARY

1. About a third of the people applying for extra rations in the autumn of 1946 were found to have tendon reflexes that were quite abnormally brisk.

2. Clinical examination revealed no other abnormalities in the neuromuscular system of eight of these people who were selected for a detailed investigation.

3. In 1946 undernutrition was found to lower the minimum galvanic current required to excite the muscles and the peripheral nerves, but no correlation was found between the briskness of the reflexes and the minimum currents required to excite. It was not possible to confirm these observations in 1947 and they may or may not have been correct.

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VIII. EMOTIONAL DISTURBANCES AND BEHAVIOURAL REACTIONS

by D. Russell Davis

Loss of weight, oedema, polyuria and other results of a diminished intake of food are described and discussed in other sections of this Report, and, although many points about them are still obscure, it is possible to state at least in outline how they arise. In addition to these classical stigmata of undernutrition, however, persons who applied for extra rations for hunger oedema frequently exhibited other symptoms and signs which were not so obviously the result of a shortage of food and yet appeared to be related to it in some way. The exaggeration of tendon reflexes (*McCance and Dean*, p. 147) is one example; the sweating syndrome (*McCance and Widdowson*, p. 1), the insomnia, the breathlessness and precordial discomfort, all of which have still to be discussed, are others. These abnormalities will now be described and each of them examined in the light of three questions: (1) Can the abnormality under consideration be satisfactorily explained on physiological grounds? Can it, for example, be the result of a deficiency of Calories or vitamins? (2) Does it conform with the similar abnormalities met with in disorders such as the neuroses, which are generally accepted to be the result of emotional disturbance? (3) To what degree is the abnormality correlated in incidence and intensity (*a*) with states that are held to result from emotional disturbance, (*b*) with abnormalities which are frankly physical in origin?

Evidence will be adduced that some or all of the abnormalities described here should be regarded as behavioural reactions or emotional disturbances brought about by the situation in which the sufferers found themselves, and an attempt will be made to analyse the situation and to indicate the most disturbing elements in it.

SUBJECTS

The persons who were examined may be divided into three groups.

1. Civilians applying for extra rations on account of hunger oedema or loss of weight. Some of the data about these people were obtained by the routine questioning at the out-patient clinic, and other information was elicited after a special interview.

2. Prisoners of war repatriated from Russia. These were also interviewed while attending the out-patient clinic.

3. Fifty-four workers and 23 staff at the I.G. Farben factory, Elberfeld, who were considered to be a representative sample of the male employees of the factory. Conditions of employment were relatively favourable, and fewer abnormalities were expected among them than among a sample representative of the whole population of German workers at this time.

THE EFFORT SYNDROME

Breathlessness, Precordial Discomfort and Allied Symptoms

Many ex-prisoners and civilians complained of constriction and oppression in the chest, stitches, precordial discomfort, palpitations and, most commonly, breathlessness. The symptoms were usually said to be provoked by slight exertion such as climbing stairs or walking uphill, but they were sometimes also

found to be troublesome while the person was lying in bed at night. They were then associated with feelings of nervousness and restlessness. The sufferers regarded these symptoms as evidence of cardiac disease, and some had reason to do so since their doctors had made a diagnosis of "Herzmuskelschwäche". This diagnosis was often mentioned by the people themselves, as was "Herzneurose".

No precise figures for the incidence of the symptoms can be given. They were rather less common in civilians than in repatriated prisoners of war; the large majority of the latter and ten of the factory employees in whom no sign of organic disease was found, complained of one or more of them in varying degree. Needless to say, a certain proportion of each of these groups showed evidence of organic disease of the heart, and a slow pulse and a low blood pressure are among the classical signs of undernutrition (Falta, 1917). Moreover, the oedema that is so often associated with severe loss of weight has been held by some to have a cardiac origin (Schittenhelm and Schlecht, 1919; Heilmeyer, 1946). Against these suggestions of primary cardiac involvement in the symptoms under consideration must be set the fact that some people with organic disease of the heart did not complain of them. The majority, moreover, of those who complained most vehemently had no signs of organic heart disease, nor had they conspicuously low blood pressures or heart rates. It is admitted that in the elderly, undernutrition and cardiac failure may often reinforce each other in the genesis of oedema, but the subjects under discussion were not old; the repatriated prisoners were all young men in what should have been the prime of life.

There is always the possibility that in some people undernutrition may affect the function of the heart or lungs in some way not yet known to us, and so give rise to the symptoms of the kind being discussed. Until that has been demonstrated, however, it seems logical to make a more conventional diagnosis. When persons exposed to an uncongenial environment complain of their hearts or of breathlessness and exhibit no signs of organic disease, it is usual to describe their condition as an "effort syndrome", and then to consider to what psychological stresses they have been subjected and how they have reacted to them. It is proposed to do likewise in this instance.

Excessive Sweating

Excessive sweating was one of the most striking features about the recently returned prisoners of war from Russia. Of a series of 200 individuals, 173 complained of it. Typically, the sweating started on the day they reached home, and 120 of them said that they first noticed it at this time. A further 39 said that it started while they were in hospital shortly before their return, when speedy repatriation was expected. Only 14 had been aware of excessive sweating for several months before their return.

The majority of the repatriated prisoners said that the sweating was worst at night, but many said that it was also provoked by any circumstance which normally produces slight sweating. Emotion, mild exertion, conversation, especially if there was cause for uneasiness, and the taking of food, even if it was cold and unseasoned, might provoke marked sweating. Sweating at night was naturally remarked upon more often if sleep was also restless and intermittent; many said that it disturbed their sleep. It occurred especially when waking from restless sleep or dreams and was associated with the heightened anxiety sometimes experienced at night; in the daytime it was brought on by worry or anxiety.

Sweating was profuse; at night it was often described as drenching. The back and chest were mentioned most frequently as the site of sweating, forehead and face less often; axillae and groins were mentioned only occasionally. During the interviews beads of sweat were seen to form on the forehead and around the nose and lips, and sometimes rivulets ran down the cheeks. The palms tended to be moist, but not strikingly so. Pale people were affected as often as the flushed.

Excessive sweating in emotional disturbance is said mainly to affect hands and feet (Kuno, 1935), and here there is a discrepancy, which cannot be neglected, between our observations and those made by others. Wood (1941a,b) stated that in effort syndrome, hands, feet, and axillae were mainly affected. Allbutt (1910) noted that the profuse sweats in neurasthenia, either by night or during the least exertion or excitement, chiefly affected the hands and feet. However, it is not at all certain that the emphasis given in the literature to the hands and feet as the site of sweating in mental disorders is justified. Davis (1946) observed sweating on the forehead in intense emotional disturbances produced experimentally. Lewis (1917) mentions palms, feet, and axillae as the site when subjects are at rest in effort syndrome, but adds, "Relatively mild stimuli, such as easy exercises or emotion, may produce conspicuous sweating of the forehead and body. In some patients a bedewed brow is almost constant." It seems likely that, whereas in the mild emotional disturbances studied by Kuno hands and feet may be mainly affected, face, forehead and trunk are the conspicuous sites when more intense disturbances are concerned.

About one-half of the civilians attending the out-patient clinic on account of their hunger oedema complained of some increase of sweating, but in none was it seen to such a degree as in the returned prisoners of war. Like giddiness and nocturia, excessive sweating was popularly regarded in Germany as a frequent effect of undernutrition, but careful questioning generally led to the conclusion that it had begun at about the same time as insomnia, irritability, and effort intolerance. The attacks of acute anxiety, which were reported by the majority of the repatriated prisoners, were only mentioned by a minority of the civilians, and this would partly account for the different incidence of excessive sweating in the two groups.

When the excessive sweating was first noted in the men coming back from the Russian prisoner of war camps it was thought to be due to tuberculosis or some other infection such as malaria, but this view was not maintained for long, since other evidences of infection were rarely found. There was no hyperpyrexia, and the basal metabolic rate did not suggest thyrotoxicosis. Attempts were made to link the effect with differences in the external temperatures in Germany and Russia, or with disturbances of water metabolism, but no evidence was found to confirm the relationships. There was no correlation of the sweating with oedema or with nocturia. It might be suggested that undernutrition in some way renders the mechanism of sweating more sensitive to stimulation, and that exertion or emotion makes this hypersensitivity manifest. Such a hypothesis is unnecessary, however, for emotional disturbance is well known to cause excessive sweating by itself even in the best nourished persons. Wood (1941a,b) stated that excessive sweating is a frequent symptom of effort syndrome and other neuroses. Jones and Tanner (1948), who made a special study of the failure of some of the British prisoners of war returning from the East to readjust themselves, demonstrated, by statistical treatment of their results, that sweating was associated with breathlessness and other symptoms which, taken

as a whole, amounted to effort syndrome. In their cases, too, sweating usually began after repatriation.

It is suggested, therefore, that the excessive sweating which was seen in the returned prisoners of war, and to a very much smaller degree among German civilians, was part of an effort syndrome, which represented a behavioural reaction to the prevailing circumstances.

Exaggeration of Tendon Reflexes

The incidence and characteristics of this sign are given by *McCance and Dean* (p. 140), and it has been shown by them that such reflexes were associated with no other abnormalities of the central nervous system. Moreover, attempts to correlate the exaggeration of reflexes with the major criteria of undernutrition have been unsuccessful. They were recorded as frequently in those who were relatively well nourished as in those who were considered on clinical grounds to be severely undernourished. They were equally common in those with and those without oedema, and they did not seem to be correlated with loss of weight, with nocturia, with the concentration of calcium in the serum or with the activity of cholinesterase. Furthermore, the character of the reflexes did not alter during the course of the experiment described by *Widdowson* (p. 313).

Examination of the applicants for extra rations, however, suggested that the briskness of the reflexes reflected a behavioural reaction to circumstances. Some of the most exaggerated reflexes were observed in the repatriated prisoners who had been subjected to severe hardships in captivity and who had returned to formidable difficulties at home. In these, and in the civilians who had remained in Wuppertal, brisk reflexes seemed to arise from a state of nervous excitement. On the other hand, those who accepted their lot with resignation or were content to get along as best they could seemed to show abnormal reflexes less often.

It seems probable, therefore, that the exaggerated reflexes were one component of an effort syndrome, in which, moreover, tendon reflexes have been said to be brisk. Lewis (1917) remarked, "A hyper-excitability of the C.N.S. appears to be very general; witness the usual and conspicuous exaggeration of the knee jerks." Allbutt (1910) wrote of a similar condition, "the 'reflexes' are never absent, on the contrary both superficial and deep are generally in well marked excess; the knee tap may make the whole body bounce, wrist taps generally produce quick responses; a triceps and a supinator reflex are often very ready. The toe bend is always flexor . . .", an apt description also of our observations.

Giddiness

It is no new discovery that undernourished people fairly commonly have attacks of giddiness. It was alluded to by Hülse (1917), Burger, Sandstead and Drummond (1945) and Heilmeyer (1946), and was discussed by Schulten (1946). The expression "faint with hunger" may refer to the same thing.

Civilian applicants for extra rations and repatriated prisoners of war complained of giddiness and about one in every four factory workers mentioned it when questioned. It was, moreover, put forward by some of the factory staff as the only possible explanation of a number of serious works accidents. The frequency of such accidents could not be established, and it must always be remembered that similar accidents occur inexplicably when there is no reason to incriminate giddiness. Several of our subjects had consulted their doctors because they feared that if they continued to work without additional nourishment an accident might result from their giddy turns; some of them

said that they had actually fallen, although minor injuries so caused were very rarely reported and, in our view, very rarely occurred in those of working age. One would therefore expect serious accidents to be correspondingly rarer.

Twenty-five repatriated prisoners who complained of giddiness were specially interviewed and examined. The age of the men varied from 26 to 52; nine of them were between 30 and 40, and twelve between 40 and 50. Their systolic blood pressures varied from 85 to 170 mm. Hg, but the majority were rather low; nine of them were 110 or less, only ten were over 120, and only one was over 140. The majority stated that their attacks had begun while they were still in Russia, but in about one-third of the subjects the attacks of giddiness appeared to have started shortly before or at the time of their return. Some thought the attacks had been more frequent when they were working in Russia, and that they were now getting better. A man would say that without any special warning or feeling of discomfort he suddenly felt a swaying sensation followed at once by flickering of his eyes, dimness or momentary blackness. All patients had their own way of stopping or shortening the attack. Fifteen said that they did so by sitting down immediately, six by holding on to something, three by lying down and one merely by standing very still. One man remembered looking up to read the destination of a tram and nothing more till he found himself lying on the road. More than half the patients became conscious of their hearts during or after an attack; twelve said that it was beating rapidly, and two complained of definite pain. In many instances sweating was associated with an attack of giddiness. It was very difficult to get any precise information about the duration of the attacks, but the majority said they lasted a few seconds, and certainly no longer than a minute; a few thought that they lasted for five minutes, one or two that they lasted longer. Fifteen men stated with assurance that the attacks were not followed by any after-effects, but the remainder were left with a feeling of tiredness or exhaustion; in three the attacks were followed by headaches. Although four men stated that the attacks were precipitated by a change of posture, this was not the common prelude. Seventeen of the men had found that their giddy turns followed moderate activity of any kind in or out of doors. The attacks as described by the civilians were so similar that they scarcely merit separate consideration.

Although Schulten (1946) and others attributed the attacks of giddiness in undernourished people solely to cardiovascular or, at any rate, to physical causes, Rook's (1947) article makes it clear that the psychological element cannot be ruled out. If one applies Rook's classification to the persons questioned in Wuppertal, none of them would appear to fall into his neurogenic group, and giddiness was much too common in Wuppertal for it to be placed in any of the epileptic syndromes. Rook also considered that both hypotension and fatigue might predispose to cerebral anaemia and a fall in intracranial pressure. If either of these conditions can induce an attack of fainting in a healthy member of an aircrew, it may certainly do likewise in any group of men suffering from undernutrition. Nevertheless in a number of the repatriated men the attacks began just as they reached home, when they were undoubtedly under great psychological stress, and the profuse sweating that was so characteristic of these men was very often stated to have begun at the same time. Their pulse rates were frequently 90–100 per minute or over when they were interviewed, which is not what one would expect in a person who is undernourished unless he is in a state of nervous tension. In addition it may be mentioned that no correlation could be found between the severity of the "fatigue" or undernutrition and the number

of attacks. One may conclude, therefore, that a psychological as well as a physical reason may have to be accepted for the attacks of giddiness that have so frequently been described in undernutrition.

Insomnia

Insomnia was a fairly common complaint among both civilian patients and repatriated prisoners of war. These people said that they were tired and sleepy in the evening and went to bed earlier than they had done in normal times. They went to sleep without difficulty and slept normally for the first part of the night, but would be roused in the middle of the night by the desire to urinate and would then lie awake, probably rising several times to pass urine, until an hour or two before it was time to get up. Then sleep would be deep, and they would get up at the last minute, feeling tired and unrefreshed. During the day they would feel sleepy and would nap whenever the occasion arose.

Lying awake was not usually regarded as unpleasant, and few seemed to worry about their inability to sleep, although they appreciated the desirability of a good night's rest. Their thoughts tended to wander over the day's work, the morrow's plans, and the difficulties of their lives. In September and October, 1946, patients seemed to spend their sleepless hours working out methods of supplementing their rations by hamstering (*McCance and Widdowson*, p. 1), and their insomnia was ascribed to their preoccupation about obtaining food. Later in the year, when hamstering had become less practicable, something else seemed to make them alert and restless.

About half the ex-prisoners to whom the question, "How do you sleep?" was put, answered "restlessly" or "badly". The majority of these men had experienced no difficulty in sleeping during imprisonment, and insomnia had begun only after their return to Germany. Many were surprised by it and attributed it to lack of familiarity with normal beds and covers. Yet sleep continued to be poor for much longer than could readily be explained in this way, even if it were a plausible explanation of insomnia for the first few nights at home. Sleeplessness among these returned prisoners of war was undoubtedly associated with excessive sweating at night.

About half the civilians who were questioned also said that their sleep was restless or bad, and about one-third of the group of factory employees described some degree of disturbance. Dreaming was not especially common and was complained of by only about 30 individuals in a series of 200. Only in three cases were dreams about food reported, and the majority of dreams were of an anxiety type in which, for example, the dreamer felt threatened by a danger not clearly perceived, was being chased and was being hampered in escaping. The setting was usually warfare, a fact which was hardly surprising.

The origin of the insomnia was probably partly physical and partly psychological. In so far as the nocturia was caused by the necessity to pass large volumes of urine, any disturbance of sleep caused by a desire to urinate must be attributed to a physical cause. Similarly, hunger pangs were sometimes troublesome at night, and people used to get up to drink cold water to suppress them. On the other hand, the salient features of the insomnia reported by our subjects—the paradox of sleepiness during the day and sleeplessness at night, and the tendency to sleep well towards the time of getting up—are the features of insomnia in the so-called fatigue states, in neurasthenia, effort syndrome and allied nervous disorders. This made it reasonable to suppose that in our subjects insomnia had a similar cause.

Fatigue and Impairment of Memory and Concentration

A large proportion of the persons interviewed complained of being tired, slack, miserable and so on. "Ich kann nicht mehr" was their common refrain. They also complained of mental and physical fatigue, inability to concentrate for anything but short periods, absent-mindedness, and lack of fluency. They felt that their mental powers were impaired and were inadequate to cope with their problems. These complaints tended to be associated with others of physical disability. They were illustrated by anecdotes about the difficulty of recollecting colleagues' names, the necessity of writing down business details that would previously have been retained in the head, the inability to read in the evenings for more than a short period, the diminishing output of work towards the end of a shift, the tendency to lose the thread in the course of a conversation and for the mind to go blank, and the difficulty of finding words in conversation or writing. As Schulten (1946) saw it, the origin of these and other symptoms was physical.

Bei länger dauerndem Hunger nehmen viele der intellektuellen Fähigkeiten mehr oder minder stark ab. Es komnt zu einer psychischen Schwerfälligkeit, Schwerbesinnlichkeit und dadurch oft auch zu einer grossen Entschlussunfähigkeit. Die Vergesslichkeit ist oft so stark, dass Erinnerungen auch aus der unmittelbaren Vergangenheit, nicht nur im Augenblick nicht bewusst, sondern völlig ausgelöscht sind. Die geistige Arbeitsfähigkeit wird dadurch noch weiter eingeschränkt, dass bei den meisten Hungerkranken bei Tage ein abnormes Schlafbedürfnis besteht, das so zwingend werden kann, dass die Fortsetzung einer geregelten Tätigkeit fast unmöglich wird. Die vielen Geistesarbeiter, die gewohnt sind, die Nachtstunden für ihre Arbeit zu benutzen, sind dazu heute nicht mehr oder unter Einsatz stärkster Energie imstande. Neben einem abnorm tiefen Schlaf, auch unter Umständen bei Tage, besteht andererseits nachts nicht selten Schlaflosigkeit, teils durch unangenehme Hungerempfindungen in der Magengegend, teils durch das häufige Wasserlassen, teils durch die allgemeinen und Nahrungssorgen, teilweise aber auch aus Gründen, die wir noch nicht kennen, also wohl als eine direkte biologische Hungerfolge.

However, attempts which were made to link these symptoms with the physical stigmata of undernutrition in the present instance were uniformly unsuccessful, perhaps partly because it was so difficult to measure the defects in performance about which complaints were made. The tests which were applied did not reveal any impairment. For instance, "tempo" was rated on clinical impressions and on the results of rough tests (e.g. counting backwards from 20 to 1), but these ratings did not correlate with such objective measures of the physical condition as the basal metabolic rate. Nor could subjects' complaints be correlated with any of the physical signs of undernutrition, and their causation remains uncertain.

Nervousness, Irritability and Restlessness

The subjective symptoms of patients and others were manifold, but for purposes of description a distinction may conveniently be made between excitement, showing itself as anxiety, restlessness and irritability, and lassitude, as typified by fatigue, weakness and inability to concentrate. The latter are the classical symptoms of undernutrition, but impatience, shortness of temper and irritability were commonly admitted at interview and, indeed, they were regarded as characteristic of the times. People were annoyed by flies on the wall, as the Germans say. Their minds were pervaded by a sense of urgency even when circumstances were relatively easy. The knowledge that others were competing for the few available amenities made people feel that their fellow-citizens were hostile, and these feelings expressed themselves in irritability.

Anxiety of this kind tended to increase at night; then it might be described as having little reference to real problems, or as a feeling of restlessness. Emotional outbursts were not uncommon in the clinic, and sometimes unfairness on the part of others was angrily denounced. Also, patients reported that

they were unduly sensitive to noise, and sometimes they were observed to respond with abnormal violence to trivial noises or other physical stimuli. When subjects were questioned about the future, their answers were coloured by alternating hopes and fears, by apprehension and foreboding; typically they said, "Can the body stand it?" or "Things can't go on like this."

In short, anxiety and restlessness, when sought for, were as characteristic a feature of the persons attending the out-patient clinic in 1946 as fatigue, weakness and inability to concentrate, and there is no doubt that they all frequently existed together in one person.

Reduction of Sexual Activity

Many of the people attending the clinic stated that their sexual interests were in abeyance, potency reduced and intercourse infrequent. Insufficient data were obtained, however, to enable these statements to be correlated with other symptoms.

More satisfactory information was obtained from the factory workers. The answers given by the married employees when asked about the frequency of intercourse are classified in Table 1. They indicate a considerable reduction in

TABLE 1

*Frequency of sexual intercourse in married factory employees**

Age (years)	Frequency of intercourse					
	1 per week or more	1 per month or more	Less often	Not at all	Total	No data
Under 50	7	15	10	12	44	3
50–60	0	5	3	12	20	4

*Consideration of the data given by Pearl (1926), Davis (1929), McCance, Luff and Widdowson (1937), and Kinsey, Pomeroy and Martin (1948), suggests that at least one-half of any group of healthy married men under the age of 50 would report that intercourse took place once a week or more often. Kinsey *et al.* give the median frequency of intercourse of married men aged 50–60 years as 0.7 per week.

a relatively large proportion of cases, and this reduction accompanied the loss of weight and the frequency of the nocturia. This makes it reasonably certain that physical factors were important causes, but they were no doubt reinforced by psychological factors. As our subjects sometimes commented, "The diet is too poor, and, besides, there are too many other things to think about." It may be added that the decline in sexual activity was not always contemporaneous with the deterioration of the diet; in some cases, it had preceded it and dated from the period of the intense air-raids on the Ruhr.

NUMERICAL DATA

The Correlation of Symptoms with Each Other and with Environmental Factors

The signs and symptoms described in the foregoing section, namely the breathlessness and precordial discomfort, the excessive sweating, the exaggeration of reflexes, the giddiness, the insomnia, the fatigue and irritability, and the reduction of sexual activity, were thought to constitute an effort syndrome and

a behavioural reaction to the prevailing environmental stresses. These hypotheses were confirmed to some extent by the correlations which were found to exist between the symptoms themselves and between the symptoms and certain environmental factors, and which were demonstrated in (*a*) patients attending the out-patient clinic and (*b*) a group of factory employees.

(*a*) *Patients.* Several experiments were made. The impression formed during the examination of applicants for extra rations, that the exaggeration of their reflexes indicated a nervous excitement induced by the stresses of their circumstances, was tested in the following manner. Some undernourished civilians and repatriated prisoners, all men under the age of 60, were selected, and their knee jerks were graded clinically. They were interviewed by another person, who did not know these gradings, and who predicted whether their reflexes were brisk or normal. The prediction was based on an evaluation of the subjects' circumstances and their psychological reaction to them, and on the degree to which their irritability, insomnia, and symptoms of effort intolerance had developed. A few subjects gave a history of chronic neurosis and for them no prediction was made. In 18 cases out of 25 the prediction proved to be correct; 6 of the 7 incorrect results were obtained when the prediction was normal (Table 2). This result gave support to the hypothesis that led to the experiment.

TABLE 2

*Prediction of tendon reflexes from interview**

Predicted		Observed	
		Brisk	Normal
Brisk ..	9	8	1
Normal	16	6	10

*The prediction bore a significant relationship to the observed grading, *P* being 0·017.

TABLE 3

Correlation between exaggeration of tendon reflexes and degree of insomnia

Subjects	Reflexes	Degree of insomnia				
		Marked	Moderate	Slight	Nil	Total
Repatriated* prisoners	Brisk	10	6	3	3	22
	Normal	2	3	5	9	19
	Total	12	9	8	12	41
Civilians†	Brisk	7	8	5	4	24
	Normal	2	5	6	9	22
	Total	9	13	11	13	46

* $\tau = 0{\cdot}418$, $P = 0{\cdot}00007$. † $\tau = 0{\cdot}313$, $P = 0{\cdot}02$.

In further similar experiments, exaggeration of reflexes was shown to be correlated with several of the abnormalities that had been taken into account in making these predictions. Thus it was found to be correlated with insomnia (Table 3), with the complaint of poor wind, which was regarded as a convenient index of effort intolerance (Table 4), and with anxiety (Table 5). In a later series of experiments exaggeration of reflexes and excessive sweating were found to be correlated (Table 6). Those whose knee jerks were graded as brisk thus tended to complain of insomnia, poor wind, anxiety and excessive sweating, and it seems reasonable to assert, therefore, that these abnormalities constituted an effort syndrome.

TABLE 4

Correlation between exaggeration of reflexes and the complaint of poor wind

Subjects	Reflexes	Degree of impairment of wind			
		Marked	Slight	Normal	Total
Repatriated prisoners*	Brisk	8	9	5	22
	Normal	4	3	12	19
	Total	12	12	17	41
Civilians†	Brisk	6	8	10	24
	Normal	2	4	16	22
	Total	8	12	26	46

*$\tau = 0{\cdot}327$, $P = 0{\cdot}02$. †$\tau = 0{\cdot}302$, $P = 0{\cdot}03$.

TABLE 5

Correlation between exaggeration of tendon reflexes and degree of anxiety

Subjects	Reflexes	Degree of anxiety			
		Marked	Slight	Normal	Total
Repatriated prisoners*	Brisk	5	12	5	22
	Normal	2	7	10	19
	Total	7	19	15	41
Civilians†	Brisk	5	9	10	24
	Normal	2	3	17	22
	Total	7	12	27	46

*$\tau = 0{\cdot}290$, $P = 0{\cdot}05$. †$\tau = 0{\cdot}292$, $P = 0{\cdot}04$.

TABLE 6

*Correlation between exaggeration of reflexes and amount of sweating**

Subjects	Amount of sweating	Reflexes					Total
		Very brisk	Brisk	Normal +	Normal	Sluggish	
Repatriated prisoners†	Excessive	7	29	32	85	5	158
	Normal	1	3	5	19	6	34
	Total	8	32	37	104	11	192
Civilians ‡	Excessive	1	2	3	0	1	7
	Normal	1	9	20	36	6	72
	Total	2	11	23	36	7	79

*In this experiment a larger series was studied; for the repatriated prisoners the data were taken from the case notes of all those attending the out-patient clinic during three periods of three months in 1946–7, and for the civilians from the case notes of a series of patients attending the clinic during the summer of 1947, because they were "underweight".

† $\tau = 0{\cdot}148$, $P = 0{\cdot}03$.

‡ $\tau = 0{\cdot}215$, $P = 0{\cdot}03$.

(*b*) *Factory employees.* This inquiry was carried out in August 1946 at the I. G. Farben factory, Elberfeld, in order to gain more information about the incidence amongst the workers of the various abnormalities observed in the applicants for extra rations attending the out-patient clinic.

Each man was questioned by one observer about housing, his family and other dependants, and his wages, by a second about his attitude to present conditions, his general circumstances and symptoms, and was physically examined by a third. Eighteen variables were dealt with in the statistical work; these did not include breathlessness or other symptoms of effort intolerance, which did not occur often enough. Only eleven variables are to be found in Table 7, however, certain others such as blood pressure and pulse rate having been omitted because their correlations have no bearing upon the present argument.

The rating of the variables was done in the following way. The sample was divided into groups of three, or in some cases into pairs, according to the previous records of sickness absence of the individuals, for it was hoped to relate these records to the findings of the experiments; as it happened, no such relations could be demonstrated. The members of each triad or pair were examined in close succession, and each man was compared in respect of each variable with the other members of the triad. Thus he was ranked A, B, or C. Now if two variables were to correspond completely, all those ranked A in one respect would be ranked A (or C) in the other respect, and those ranked B and C in one would be ranked respectively B and C in the other (or B and A). A measure of the actual correspondence was obtained after the manner of Kendall's (1943) τ coefficient, the details of the statistical method being adapted by Whitfield

(1947) for the purpose of the experiment. In arriving at the coefficients given in Table 7 age was allowed for, and the coefficients are partial ones.

The following variables have been included: (1) Difficulty of circumstances. The rating was unfavourable in the presence of such things as invalidism or incompetence in the wife, poverty because of abnormal liabilities or, especially, poor housing conditions, and favourable when there were, for example, special advantages for obtaining extra food or in large households where several members contributed to the economy. (2) Adaptation to circumstances. This rating was based upon assessments of the subject's attitude to prevailing circumstances. (3) Continuation of inessential activities. The rating of this variable was based on an evaluation of spare-time activities and was high if the individual participated in activities that were not essential to the maintenance of a minimum standard of living. Housework, gardening and spare-time work for pay were not taken as inessential. The variables (4) complaints of ill-health, (5) complaints of mental inefficiency, (7) nocturia, (8) frequency of coitus, (9) insomnia and (10) briskness of tendon reflexes do not require further explanation. The factor (6), weight loss, refers to the difference between actual weight and the weight prescribed for the age and height of the individual by the Hassing-Schall scale. The factor (11), score on a dynamometer test, refers to the sum of the scores of three trials on a dynamometer measuring strength of hand grip.

Since the coefficients given in Table 7 are partial ones, no test of significance can be applied, and conclusions have to be based upon their relative sizes. Coefficients of less than 0·280 have been left out of the Table since this value was judged to be the margin of significance. Before drawing any conclusions from the Table, however, the results of a further inquiry will be presented.

TABLE 7

Factory employees: Partial τ correlations keeping age constant*

Variables	1	2	3	4	5	6	7	8	9	10	11
1. Difficulty of circumstances	—	0·293	0·287	—	—	—	0·371	0·297	0·371	0·311	—
2. Adaptation to circumstances ..	0·293	—	0·333	—	—	0·346	—	—	0·349	—	0·327
3. Continuation of inessential activities ..	0·287	0·333	—	—	—	—	—	0·314	—	—	—
4. Complaints of ill-health	—	—	—	—	0·401	—	—	—	0·355	—	—
5. Complaints of mental inefficiency	—	—	—	0·401	—	—	—	—	—	—	—
6. Weight loss ..	—	0·346	—	—	—	—	0·360	0·295	−0·303	—	—
7. Nocturia	0·371	—	—	—	—	0·360	—	0·501	—	—	—
8. Frequency of coitus	0·297	—	0·314	—	—	0·295	0·501	—	—	—	—
9. Insomnia	0·371	0·349	—	0·355	—	−0·303	—	—	—	—	0·403
10. Briskness of tendon reflexes	0·311	—	—	—	—	—	—	—	—	—	—
11. Score on dynamometer test	—	0·327	—	—	—	—	—	—	0·403	—	—

*Only coefficients of more than 0·280 have been included. The coefficient is positive when both factors have varied together in the expected direction. Only that between (6) and (9) is negative.

The rating of the variable (2), adaptation to circumstances, was not entirely satisfactory, for among those who were judged to be comparatively poorly adapted were individuals showing different modes of abnormal or inefficient reaction, when it had been supposed from experience in the examination of patients that certain symptoms, such as insomnia, were the outcome of only one particular mode of reaction, the so-called "overactive" reaction. This point was anticipated in the planning of one of the interviews, and the reaction of each man to the demands made upon him was classified as either "efficient", "overactive", or "inert".

Those rated as efficient retained a degree of confidence in their ability to deal with their adversities and usually managed to secure sufficient amenities to

TABLE 8

*Factory employees: Type of behavioural reaction and rating of other variables**

Variable	The overactive compared with the efficient	The inert compared with the efficient
1. Difficulty of circumstances	0·316 The overactive tend to have more difficult circumstances ($P = 0·01$)	—
2. Continuation of inessential activities	—	—
3. Complaints of ill-health	—	—
4. Complaints of mental inefficiency	No difference	—
5. Weight loss	No difference	—
6. Nocturia	0·370 The overactive tend to have more nocturia ($P = 0·003$)	—
7. Frequency of coitus ..	0·336 The overactive tend to have less frequent coitus ($P=0·01$)	—
8. Insomnia	0·351 The overactive tend to have more insomnia ($P = 0·02$)	—
9 Briskness of knee jerks ..	0·307 The overactive tend to have brisk reflexes ($P = 0·02$)	—
10. Score on a dynamometer test	0·212 The overactive tend to make lower scores ($P = 0·05$)	0·282 The inert tend to make lower scores ($P = 0·01$)

* τ Correlations by the method of Whitfield (1947).

make life tolerable; they were not discontented, distressed or worried. On the other hand, to those rated as overactive the attainment of even the minimum of amenities seemed to demand urgent measures, and they felt inadequate to deal with the many difficulties that beset them. They felt it necessary to exert themselves constantly, and tended to be alert and apprehensive. The inert were resigned to a low level of existence and seemed to have given up the struggle to improve their position. They tended to rely on the exertions of wife and relatives.

These ratings were correlated with those of the other variables by the method Whitfield devised (1947) for cases in which one variable is ranked and the other dichotomous. Thus the efficient were compared with the overactive and with the inert. The results are shown in Table 8. These correlation coefficients were normal ones, and tests of significance could be applied, since age was allowed for by treating each age decade separately (the values of S and V being summed). Only the significant coefficients are given. The classification of reaction and the rating of the variables 1, 3, 4, 5, 7, 8, and 9 were made by the same observer, and cannot be regarded as independent, although this observer was not aware of the hypotheses that were being tested. The following conclusions can be drawn from the results presented in Tables 7 and 8.

(*a*) Insomnia is correlated with the reaction of overactivity, but not with that of inertia. The relatively high correlation with variable (1), difficulty of circumstances, also supports the hypothesis that insomnia is a behavioural reaction to environmental stresses, and that it is not, like weight loss and nocturia, a physical consequence of undernutrition. Indeed, insomnia is not correlated with nocturia at all, and the greater the weight loss, the less disturbed did sleep tend to be.

(*b*) The correlation of exaggeration of tendon reflexes with difficulty of circumstances and with the overactivity reaction suggests that exaggeration of reflexes is a manifestation of the behavioural reaction of overactivity and is not attributable to undernutrition directly.

(*c*) The inverse correlation of frequency of coitus with difficulty of circumstances, continuation of inessential activities, the overactivity reaction and with loss of weight and nocturia suggests that reduction of sexual activity is both the outcome of overactivity and a direct consequence of undernutrition.

The finding that the scores on a dynamometer test correlate with both abnormal modes of reaction is not of major significance, but it gives support to the hypotheses under test. The tendency of the overactive to urinate frequently at night is no doubt a result of the restlessness associated with this mode of reaction and does not indicate a greater degree of polyuria.

DISCUSSION

Physical and Behavioural Effects

Clinical and statistical data have been collected to determine whether some of the common symptoms of undernutrition were primarily the results of a physical dietary deficiency or part of a behavioural reaction to external circumstances, and evidence has been produced to show that many of the symptoms associated with undernutrition, such as insomnia, sweating and breathlessness, may be regarded as primarily behavioural. It is important to decide upon the origin of these symptoms, because treatment depends so much upon it. The problem is not confined to Germany, since the majority of the

symptoms that have been described are widespread in every modern community. At one time they were attributed to neurasthenia; they are now called effort syndrome when they occur in soldiers; in the less marked form in which they are rife in a civilian population they constitute what was recently called "post-war fatigue" by the popular press and the pharmaceutical firms. The names are ephemeral but the symptoms are perennial. In Germany they were merely more prominent, more frequent and more intense in 1946–7 than they are at present in Great Britain. There is an obstinate belief, which survives repeated disappointment, that such symptoms can be removed by tonics, glycerophosphates, vitamins or whatever other treatment is in fashion—in Germany it was the restoration of a "proper" balance of fat and protein in the diet—and this belief springs from the idea, still held, that such symptoms result from a general or nervous metabolic disturbance, which can be put right by chemical means. *Prima facie* the symptoms in Germany might have been thought to have had a metabolic cause, since they were so striking when there was an obvious dietary deficiency. This argument depends upon the correlation of increases or decreases in the severity of these symptoms with similar alterations in the food supply, but it may be fallacious, for it does not take into account the possibility that as the diet deteriorates other environmental stresses may increase and give rise to the behavioural effects. The argument, nevertheless, is an attractive one to those who believe in the physical origin of the symptoms. It cannot, however, be accepted in its entirety, and it is suggested that the symptoms were the product of the setting in which the undernutrition developed rather than the direct result of the shortage of food itself.

Causes of the Symptoms

The general population. The civilians sent to the clinic were a selected group. Although some of them complained of housing difficulties, and although for some food took a second place to fuel during the cold winter of 1946–7, the great majority stated that their chief worry was the shortage of food. Most of them said that they were always hungry, but when they were asked to explain what hunger meant to them, several distinct elements could be recognized in their answers. Hunger pangs were emphasized only by about one person in four. Nearly every answer contained some reference to appetite, which may be taken to imply a healthy desire for food with the anticipation of getting it. To the majority, however, hunger meant much more than a desire for food to satisfy a temporary physiological need. It represented a threat to their well-being, and was associated with frequent appraisals of the degree of undernutrition that they could tolerate, and the fear that they might not survive. Apprehension was greatest in those who felt unable to meet the situation, and this was illustrated by the character of some of the dreams that were reported. In fact their "hunger" had implications much wider than the momentary satisfaction of bodily wants.

The complexity of the problem is illustrated by some observations which were made during the experiment described by *Widdowson* (p. 313). On admission to hospital all the subjects of this experiment complained of intense and constant hunger, but none of them felt hungry on the unlimited diet that was provided for them for the next eight weeks. It had been expected that intense hunger would at once return when the plentiful diet came to an end, but this was not so. Only two subjects felt hungry during the first few days after discharge and only one-half of the group at the end of the first fortnight. Yet all had lost

weight at the end of the fortnight and continued to do so. Only after fourteen weeks did all complain of hunger as intense as it had been before the feeding began. Thus an insufficient diet was not by itself a cause of hunger. It seems reasonable, therefore, to suppose that the individual's attitude to general circumstances was also involved, and that this in turn was partly determined by feelings of weakness arising directly from the dietary deficiency.

One of the men in the factory experiment stated that he had been intensely hungry till a few weeks before, when the first of what was taken to be a series of food parcels arrived from America. Shared out in a family of three, the nutritional value of one parcel could not have been great, and the subject's weight had not changed. He said, however, that his physical condition had improved considerably, and this must be attributed to the psychological rather than the nutritional value of the parcel. Of the six subjects in Widdowson's experiment whose weights were within 4 kg. of their "Sollgewicht", but who complained of hunger, certainly three, and possibly five, were especially worried about their general well-being.

Incidentally, a few striking instances of subjects denying that they were hungry although their nutrition was very poor were met with at the clinic. This attitude seemed to be associated with a considerable reduction in the tempo of mental and physical activity, and was thought to be due to a relatively large fall in the basal metabolic rate. Four typical cases of this kind were selected and their basal metabolic rates were found to be −48 per cent, −32 per cent, −20 per cent, and −6 per cent. Thus three of the results fulfilled expectation, but there are not enough data to draw any definite conclusions.

The German population had been accustomed to living in a world in which there was a sufficient supply of food and a system for distributing it. The shortage of food and the breakdown of communications forced people to adopt irregular methods of obtaining supplies (*McCance and Widdowson*, p. 1). The method mainly adopted by our subjects was hamstering. People set out prepared to travel long distances and suffer many privations without any certainty that they would obtain sufficient food to make the expedition worth while. Many were loath to go hamstering, but the well-being of a family depended upon success in it. To achieve success the individual had to be constantly alert for opportunities, and hamstering thus tended to be a matter of preoccupation and worry.

Personal success in supplementing the official rations became of the greatest importance, and success in other spheres of activity of more value to society took second place. Standards of morality were abandoned under the influence of hunger. Many people, for instance, did not regard stealing as morally wrong for a hungry man. People became secretive about their activities, and they no longer trusted to the kindness or good faith of anyone outside the family. All these factors caused a loss of confidence in the security and benevolence of the social environment.

Repatriated prisoners of war. These men had a background very different from that of the civilians. After a shorter or longer time in the army they had been captured, herded like animals and made to work on insufficient rations till they were unable to work any more. Physical failures, with the label O.K. ("ohne Kraft"), they had been sent back to their own country to find themselves faced with the problems and decisions inseparable from individual responsibility in any civilized community, but magnified for them by the internal disorganization of Germany. Many of the prisoners of war who returned to Great Britain

suffered from a lack of confidence, but the circumstances of their return, often by air, to a victorious and relatively prosperous country were very different, and restoration of confidence was usually rapid. In the small proportion, however, for whom psychiatric treatment was required, the clinical picture was not unlike that seen in Wuppertal (Jones and Tanner, 1948). Little was done to help these repatriated Germans to rehabilitate themselves. They were as a rule provided with plenty of food so that hunger in its narrow sense could not have been a cause of the symptoms they developed. They were, however, treated as semi-invalids by their doctors and relations. They lay in bed and ate extravagantly till they became very fat, and attempts to obtain work were generally discouraged. There is little wonder that most of these men should have lost all confidence in their ability to take charge of their own futures. It is to these causes rather than to hunger that their sweating, giddiness, "Herzklopfen" and other symptoms of effort syndrome and anxiety seem to have been due.

SUMMARY

1. Many of the symptoms and signs that were commonly seen in civilians and repatriated prisoners were not directly attributable to undernutrition, although they were often associated with it.

2. There would seem to be a psychological as well as a physical cause for the breathlessness, sweating, insomnia, giddiness, exaggerated reflexes, fatigue, impairment of memory and other complaints.

3. All these symptoms can be regarded as components of an effort syndrome.

4. It is suggested that among the German civilians the stresses accompanying the shortage of food were the main underlying causes of anxiety, and hence of the signs of effort syndrome.

5. The treatment they received in Russia and the difficulties facing them on their return seem to have provoked the symptoms in the repatriated prisoners.

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IX. THE EFFECT OF UNDERNUTRITION AND OF POSTURE ON THE VOLUME AND COMPOSITION OF THE BODY FLUIDS

by E. M. Widdowson and R. A. McCance

In the course of the work in Wuppertal many minor investigations were made to study points of interest or to clear up uncertainties in technique. Some of these produced important results, and a number of them, which directly concerned the fluids of the body or their constituents, have been collected together in this paper. The literature bearing on this problem has been fully discussed by *McCance* (p. 21).

THE EFFECT OF UNDERNUTRITION ON THE SIZE OF THE FLUID COMPARTMENTS OF THE BODY

Subjects and Methods

The subjects used for the investigation were five healthy men between 32 and 50 years of age who were members of the Unit, five German men who were admitted to the hospital at Wuppertal-Barmen for studies of their serum cholinesterases (*Hutchinson, McCance and Widdowson*, p. 216), and ten repatriated prisoners of war. The Barmen subjects were undernourished but not seriously so. Two tests were made on the men repatriated from Russia; the first immediately after their repatriation, while they were still somewhat wasted, and the second after they had had plenty to eat for eight weeks and had each gained about 15 kg. in weight. The extracellular water was measured by the thiocyanate method (Lavietes, Bourdillon and Klinghoffer, 1936; *Appendix* p. 401). The total body water was assessed by measuring the rise in the concentration of urea in the body fluids after the ingestion of urea. A sample of blood was taken from the lobe of the ear and urine was collected over a two-hour period; each man then took by mouth 25 g. of urea dissolved in a little water. Blood and urine were collected after 40, 80 and 120 minutes, and the urea in the urine and in the water of the blood was estimated. A curve representing the changes in blood urea was drawn for each man; the curves showed that the maximum concentration was usually reached 60–80 minutes after the dose was taken. It was assumed that the "endogenous" urea excretion continued at the same rate as in the control period, and the amount of the ingested urea remaining in the body at various times after all the urea had been absorbed was calculated by subtracting the amount of the excess excretion from the amount of the dose (25 g.). From the figures so obtained, and the rise in the concentration of urea in the water of the blood, the volume of fluid in which the urea was dissolved was calculated. The cell water was obtained by difference.

Results

Table 1 shows the results that were obtained on the normal men and the Barmen subjects. The normal men all had less extracellular water than the others, and the average was raised by the first man who was exceptionally thin and light for his 5 ft. 10½ in., and for whom the values obtained stood between those of his four companions and the undernourished men. The excess of thiocyanate space in the undernourished men was to be expected from previous

TABLE 1

The total extracellular and cellular water in normal and undernourished men

Subject	Weight (kg.)	Total water as percentage of body weight	Extracellular water as percentage of body weight	Cell water as percentage of body weight
Normal				
1	56·3	67·8	25·5	42·3
2	73·5	58·8	20·6	38·2
3	62·8	58·0	21·2	36·8
4	62·1	63·3	22·7	40·6
5	68·5	61·0	19·4	41·6
Average	64.6	61·8	21·9	39·9
Under-nourished				
B57	60·4	65·6	27·0	38·6
B176	63·9	60·5	25·6	34·9
B238	49·0	61·0	25·9	35·1
B239	68·3	59·2	27·3	31·9
B240	58·5	64·2	25·8	38·4
Average	60·0	62·1	26·3	35·8

work. The normal men contained more cell water per unit of body weigh than the Barmen subjects, which was presumably an expression of the fac that their bodies contained a greater proportion of muscular and glandula tissues.

Table 2 shows some of the results that were obtained on the repatriate prisoners of war. It will be seen that the total body water was high on thei return and averaged 69·3 per cent of their weight. Eight weeks later this figur had fallen to 57·3, and the reduction had taken place almost entirely at th expense of the extracellular fluid. These changes were larger than the difference between the normal and the Barmen subjects. The figures for the repatriate prisoners suggested that a number of them had still not reduced their extra cellular fluid to a normal proportion of their body weight by the time th second measurement was made. The Table also shows the clinical grading of th oedema in these men. Three of them had no oedema at any time, one had mor at the beginning, and four more at the end. The appearance or accentuation clinical oedema on return to a generous diet is an observation that has bee made on other occasions (*Widdowson*, p. 313), and these experiments show tha the degree of oedema detectable clinically may bear very little relation to th changes in thiocyanate space which are such a fundamental feature of unde nutrition. In well-nourished and normally proportioned people the ratio extracellular to cellular fluids is fairly constant and is unaffected by the depos tion of fat (McCance and Widdowson, 1951). This ratio is altered by undernutr tion, and it is probable that during the recovery of these men fat refilled par of the body which had been occupied by extracellular fluid during the perio of undernutrition.

TABLE 2

Effect of abundant food with a large increase in body weight on the partition of body water

Subject	On return from Russia					Eight weeks later				
	Weight (kg.)	Clinical oedema grading	Total water as percentage of body weight	Extracellular water as percentage of body weight	Cell water as percentage of body weight	Weight (kg.)	Clinical oedema grading	Total water as percentage of body weight	Extracellular water as percentage of body weight	Cell water as percentage of body weight
Nag.	61·0	1	66·0	30·2	35·8	75·8	0	56·7	20·4	36·3
Nab.	62·0	0	69·2	34·3	34·9	82·7	1	58·0	24·7	33·3
Mai.	55·0	0	70·8	40·5	30·3	73·0	1	60·0	27·0	33·0
Wil.	58·0	0	71·7	34·5	37·2	70·7	0	55·3	18·5	36·8
Str.	58·0	0	67·7	39·5	28·2	74·6	0	54·0	23·7	30·3
Sch.	67·4	1	71·8	41·8	30·0	84·5	1	57·5	26·4	31·1
Nob.	48·0	0	68·8	34·8	34·0	61·4	0	55·8	23·2	32·6
Elf.	56·0	1	66·6	40·7	25·9	69·2	1	56·0	20·6	35·4
Pac.	57·5	0	67·8	43·5	24·3	69·9	1	62·0	28·5	33·5
Kar.	52·5	0	72·5	46·2	26·3	67·7	1	57·7	26·0	31·7
Average	57·5		69·3	38·6	30·7	72·9		57·3	23·9	33·4

Table 3 gives an analysis of the gain in weight of these repatriated prisoners of war. It will be seen that, in spite of the big fall in the body water expressed as a percentage of the body weight, there was on the whole an increase in the absolute amount of water. There was a decrease, absolute as well as relative, in the volume of extracellular fluid, and a considerable increase in cell water. If

TABLE 3

Analysis of the gain in weight of repatriated prisoners of war

Subject	Gain or loss in body water:			Gain in:	
	Total water (l.)	Extracellular water (l.)	Cell water (l.)	Muscle (kg.)	Fat (kg.)
Nag.	+2·8	−2·9	+ 5·7	8·5	9·2
Nab.	+5·1	−0·9	+ 6·0	8·9	12·7
Mai.	+4·8	−2·6	+ 7·4	11·0	9·6
Wil.	−2·4	−6·9	+ 4·5	6·7	12·9
Str.	+1·0	−5·2	+ 6·2	9·3	12·5
Sch.	+0·2	−5·9	+ 6·1	9·1	13·9
Nob.	+1·2	−2·5	+ 3·7	5·5	10·4
Elf.	+1·5	−8·5	+10·0	14·9	6·8
Pac.	+4·1	−5·1	+ 9·5	14·2	3·3
Kar.	+1·1	−6·7	+ 7·8	11·6	10·3
Average	+2·0	−4·8	+ 6·8	10·1	10·2

it is assumed that all this water had been devoted to increasing the cell mass, and that this contains 67 per cent of water, one arrives at the approximations shown in the last two columns of the Table. These figures show that appearances may be very deceptive, for clinically the men seemed to gain nothing but fat. The whole question has been further discussed and elaborated by McCance and Widdowson (1951). The gains in nitrogenous cell matter were substantiated by balance experiments (*Widdowson and Thrussell*, p. 296).

A COMPARISON OF THE VOLUMES OF OEDEMA AND EXTRACELLULAR FLUID

It has just been shown that the changes in clinical oedema may bear no relationship to the much more fundamental changes in thiocyanate space that may be going on at the same time. It was felt that more information of a quantitative nature was required about this matter, and accordingly some further experiments were organized to compare the volumes of measurable clinical oedema with the size of the thiocyanate space.

The eight subjects were applicants for extra rations on account of hunger oedema at the Städtisches Krankenhaus, Wuppertal-Barmen, and their ages ranged from 34 to 58. One (B168) was a woman. The degree of clinical oedema varied. One man had no oedema, one had grade 4 (*McCance and Widdowson*, p. 1), and the others intermediate amounts. The subjects were admitted in the evening and their oedema was graded clinically by one person. Another person then measured the volume of their legs below the knee by the displacement of water, as was done for the measurement of arms by *McCance and Thrussell*

(p. 276). The subjects were then put to bed and kept there till 10 or 11 a.m. the following day, when the volume of their extracellular fluid was estimated by thiocyanate; their oedema was again graded, and their legs measured, by the same people who had made the observations on the previous evening. The intake of fluid and the volumes of urine passed during the period covered by the tests were measured, but the measurements of intake and output, which were actually very similar, did not yield any useful information, probably because the whole diet of the patients, including its mineral constituents, was altered when they were admitted to hospital.

TABLE 4

The comparative volumes of oedema and extracellular fluids

Subject	Weight (kg.)	Volume of extracellular fluid as percentage of body weight	Grading of oedema		Decrease in volume of legs:	
			Night	Morning	c.c.	As percentage of body weight
B88	59·0	28·4	4	1	950	1·6
B160	71·0	28·3	3	0	475	0·7
B163	73·0	28·6	1	0	400	0·5
B166	59·5	30·7	0	0	0	0
B167	67·0	28·2	2	0	250	0·4
B169	58·0	30·8	3	0	270	0·5
B170	62·0	28·8	2	0	255	0·4
B168 (F)	60·0	32·7	3	1	240	0·4

The results are shown in Table 4. The volumes of extracellular fluid were considerably higher than normal, which is generally reckoned to be about 21 per cent of the body weight, but they were lower than those of the repatriated prisoners of war shown in Table 2, who had, on the whole, much less oedema. The changes in the clinical grading of the oedema did not follow closely the measured changes in the volume of the legs recorded over the same period. A more noteworthy finding, however, was the small amount of oedema fluid in these legs when compared with the total, or even the excess, extracellular fluid in the body. These results demonstrate once more that clinical oedema is no measure of undernutrition or even of the excess of extracellular fluid carried by an undernourished person.

THE CONSTITUENTS OF THE BLOOD

A mild degree of anaemia and a low concentration of serum proteins have been described many times as characteristic features of undernourished communities, and it is probably true to say that a statistical treatment of the subject would usually show a fairly good correlation between the degree of undernutrition and the extent of the fall in erythrocytes and serum proteins unless there were some complicating factors such as hookworm infestation or specific deficiencies. Many estimations of haemoglobin and plasma proteins have, however, been made from time to time by people who did not realize how difficult and how important it was to standardize the conditions under which the blood was withdrawn. At least two variables have nearly always been disregarded and it is proposed to discuss them in this section. The effect of one of them, posture,

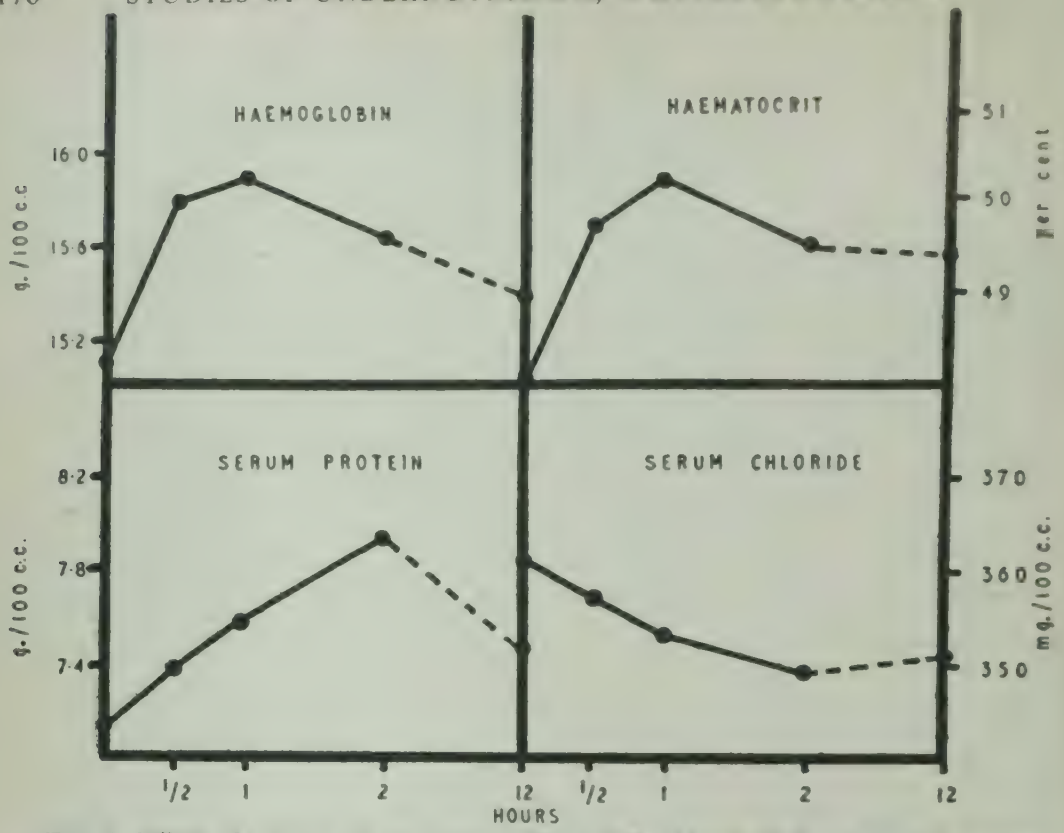

FIG. 1. Effect of posture on the composition of the blood of three normal persons. First sample taken before rising from bed in the morning; second, third and fourth samples taken after standing still for ½, 1 and 2 hr. respectively; fifth sample taken in the evening. Results averaged for three subjects.

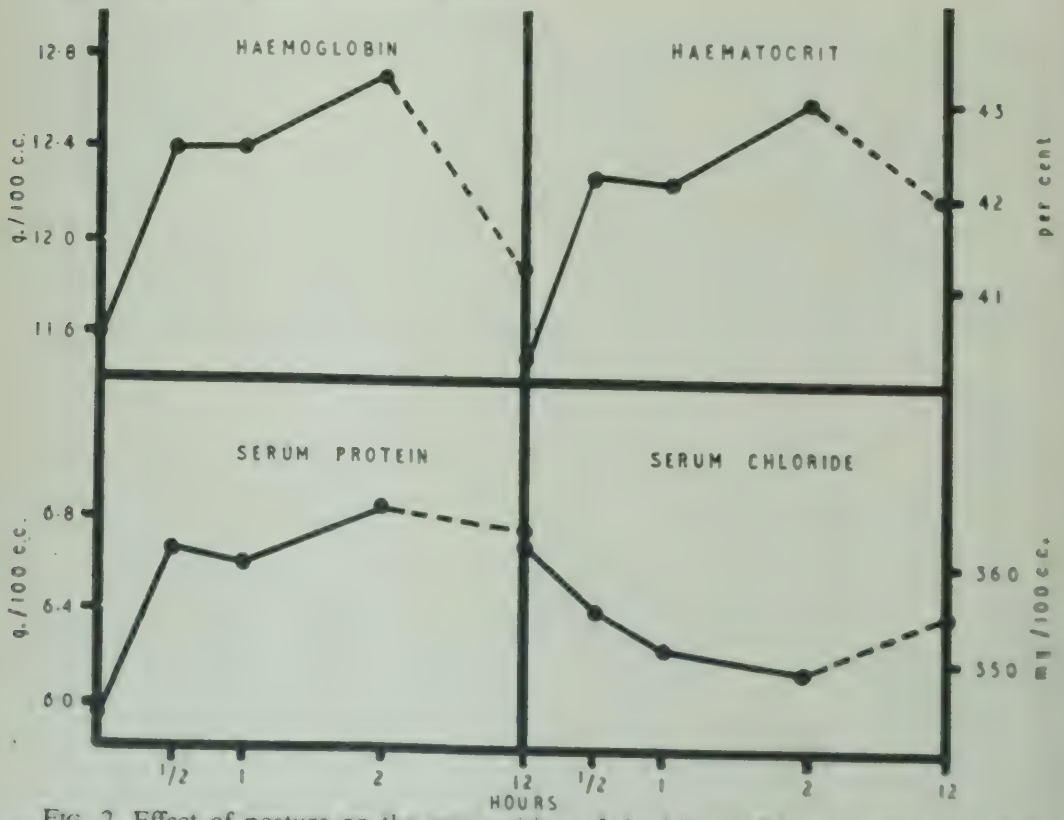

FIG. 2. Effect of posture on the composition of the blood of four German subjects. First sample taken before rising from bed; second, third and fourth samples taken after standing still for ½, 1 and 2 hr. respectively; fifth sample taken in the evening.

has been described before, but few workers have realized how many of the serum constituents may be involved. The effect of the other has not hitherto been considered.

Effect of Posture

The experiments involving change of posture were carried out on both normal and undernourished subjects. Serial estimations were made on the constituents of the blood. The exact procedures were as follows: (1) Blood was withdrawn without stasis from three normal and four undernourished persons while they were still in bed in the morning. The subjects then rose, put on their clothes and stood quietly for two hours. Blood was taken ½, 1, and 2 hr. after they had

FIG. 3. Effect of posture on the composition of the blood of two German subjects. First sample taken after standing still for 45 min.; second, third, and fourth and fifth samples taken after lying in bed for ½, 1, 2 and 12 hr. respectively.

got up, and again in the evening after they had been up and about all day. (2) Blood was taken from two undernourished German men after they had risen from bed late in the afternoon and stood quietly for 45 minutes. The two men then lay down and blood was taken after ½, 1, and 12 hr. Figs. 1 and 2 show the averaged results that were obtained by the first procedure on the three normal people and the four undernourished subjects, and Fig. 3 the averaged results given by the second procedure.

There can be no doubt about the rapid rise in serum proteins, haemoglobin and haematocrit that occurred when the subjects stood up (Figs. 1 and 2), and these changes have been described and discussed before. The literature on the serum proteins has been summarized by *McCance* (p. 21). The tendency of the concentrations to return to their initial values after one hour and the further fall that occurred during the course of the day do not seem to have been described by

others. The changes in serum chloride have not previously been described in man, but they were to be expected on physico-chemical grounds, and Darrow, Hopper and Cary (1932) observed such changes in the serum of a dog. Fig. 3 shows that changes in the opposite direction were equally easily obtained, and may have been magnified because the first sample of blood was taken after the men had been standing for 45 minutes, i.e. when the concentrations were likely to have been at their highest. The magnitude of these changes in haemoglobin, haematocrit, and serum proteins requires no emphasis.

TABLE 5

Effect of posture on the serum calcium and magnesium

	Undernourished subjects		Normal subjects	
	Up and about	Before rising	Up and about	Before rising
Average serum calcium .. (mg. /100 c.c.)	10·29	9·86	10·31	10·14
Standard deviation ..	0·43	0·45	1·06	0·53
Average serum magnesium (mg./100 c.c.)	2·17	2·11	2·22	2·21
Standard deviation ..	0·11	0·10	0·11	0·12

In another study the effects of posture on the serum calcium of 14 undernourished and 12 normal people were investigated. The serum magnesium was also followed in 7 of the undernourished and 9 of the normal people. The results, which are shown in Table 5, indicate that there was no real difference between the normal subjects and the undernourished. In both groups the serum calcium averaged 10·3 mg./100 c.c. in the upright and less in the recumbent posture. The changes in the normal subjects were small, but in the undernourished subjects the difference between the two findings was statistically significant ($t = 5{\cdot}90$, $P = <0{\cdot}01$), and it is worth noting that had the blood been taken from the normals when they were up and about and from the undernourished when they were recumbent, the conclusion might easily have been drawn that undernutrition lowered the serum calcium. Neither undernutrition nor posture sensibly altered the levels of serum magnesium. There is a long literature dealing with the relative levels of serum calcium and serum proteins, and if a significant part of the calcium is attached to the serum proteins, the above results are easy to understand. They are perhaps important because they indicate the need for standardizing all the experimental conditions when small departures from the normal are under investigation.

Effect of Rest in Bed

These experiments were originally planned because of the uncertainty about the volume of the plasma in persons with hunger oedema. The problem, which has been discussed by *McCance* (p. 21), may be summarized in this way. If oedema is due to overfiltration from the capillaries the plasma volume should be below normal in persons with hunger oedema; yet several workers have reported that the plasma volume is not low, but high, and that it falls as patients lose their oedema in the first few days of treatment; and it has been implied, therefore, that the plasma shares in the general overhydration of the body. With

the idea of extending these observations, 12 undernourished men, most of whom had some oedema, were admitted to hospital during the morning, and were put to bed after their midday meal. Two hours later, venous blood was collected without stasis, and the haemoglobin, haematocrit and serum proteins were determined. The men remained in bed for three days, getting up only to empty their bowels. On the fourth morning they got up, stayed up all the morning until after dinner, then went to bed at the same time as they had done on the first day, and were again bled after two hours. The determinations on the blood were repeated.

TABLE 6

Effect of rest in bed on the body weight, haemoglobin and serum proteins of 12 undernourished men

	Weight (kg.)	Haemoglobin (g./100 c.c.)	Haematocrit (per cent)	Serum proteins (g./100 c.c.)
On admission (average) ..	64·2	13·33	42·3	6·26
Standard deviation		1·11	3·74	0·29
Three days later (average) ..	63·8	14·12	46·3	6·55
Standard deviation		1·78	3·85	0·57

After the men had been in bed for three days, oedema had almost or entirely disappeared, and the results of the two sets of determinations are summarized in Table 6. They are interesting for two reasons: (1) The treatment described undoubtedly raised the levels of haemoglobin, haematocrit and serum proteins, and it is almost certain, therefore, that the serum volume fell. The result, however, was the same whether the subject had clinical oedema or not, and in one of the men, who had no clinical oedema on admission, the haemoglobin rose from 12·55 to 13·73 g. per 100 c.c., the haematocrit from 38·7 to 43·6 per cent, and the serum proteins from 6·5 to 6·8 g. per 100 c.c. (2) In spite of the loss of clinical oedema and the signs of a fall in the volume of the serum, there was no significant change in the subjects' body weights, and they could not, therefore, have been getting rid of their superfluous fluid by excreting it. Similar experiments were, therefore, carried out on well-nourished men, and the results obtained were very similar to those which have just been described (Widdowson and McCance, 1950). It is, therefore, probable that the change in the volume of the plasma observed in these experiments on undernourished people with or without oedema was due, not to the excretion of oedema fluid, but to the effect of rest in bed on the distribution of the body fluids, and that in consequence the interpretation of many of the earlier experiments may not have been correct.

Taking these results as a whole it is clear that posture must be carefully controlled if the concentrations of many of the constituents of the blood in any two groups are to be compared, and that in giving any values for haemoglobin or serum proteins it is essential to state whether the person was standing or lying down when the blood was taken. It is also necessary to specify for how long he had been in that position.

SUMMARY

1. In undernutrition the body was found to contain an excess of extracellular fluid.

2. During the recovery of undernourished prisoners of war there was a fall in the percentage of extracellular fluid, and also of the total fluid in the body. There was a gain of 15 kg. in weight, and this was due to an increase in the amount of cell water (and protein), and to a deposition of fat. There was a decrease, absolute as well as relative, in extracellular fluid.

3. The oedema which could be seen and felt in the legs usually represented only a small proportion of the total excess of extracellular fluid in the body.

4. Standing up for 1½ hours after spending some time recumbent (*a*) raised the haematocrit and concentrations of haemoglobin in the blood, (*b*) raised the concentrations of serum proteins and of calcium, and (*c*) lowered the concentration of serum chlorides.

5. Lying down for 1½ hours had the reverse effect, but rest in bed for three days raised the haematocrits and concentrations of haemoglobin. This considerable but hitherto undescribed effect has probably led previous investigators into drawing erroneous conclusions.

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X. ASPECTS OF RENAL FUNCTION AND WATER METABOLISM

by R. A. McCance

THE function of the kidney has been investigated many times in undernourished people, and it is certain that there are no signs of nitrogen retention in the body fluids. Only Maase and Zondek (1917a,b) have ever reported abnormal blood ureas, or "R.N.". The absence of albuminuria has always been one of the points in distinguishing inanition oedema from other types, and water excretion and simple concentration tests were carried out by a number of investigators during the first world war (Schittenhelm and Schlecht, 1918, 1919). The excretion of water after a test dose was generally found to be normal, and so was the excretion of salt. Urines were normally concentrated if the tests were made at a suitable time, i.e. when the patients were not in the process of excreting large volumes of oedema fluid. In general these results have been confirmed by subsequent investigators (Gsell, see Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948). Schwarz (1945), who investigated some people in a state of advanced undernutrition, found their renal function tests to be only 20 per cent of normal, and their powers of concentration and of dilution also to be impaired even after the oedema had gone, but Mollison (1946) found perfectly normal inulin and diodone clearances in two very emaciated people without oedema, and inulin clearances of 80 c.c. and 53 c.c. per 1·73 sq. m. per min. in two equally emaciated people with oedema.

In 1942 Govaerts and Lequîme published their observations on the effect of posture on the urine flow of undernourished persons. They showed, as many others had done before them, that rest in bed led to a considerable diuresis, and their comment on this was: "Cette circonstance indiquait qu'il devait exister chez eux une exagération de l'influence qu'exerce la station debout sur l'excrétion urinaire." They also showed that persons with oedema passed more urine after drinking a litre of water in bed than they did after drinking the same volume when they were up and about. Govaerts and Lequîme, therefore, seem to have known that the volume of urine produced by normal people was affected by posture and to have believed that this effect was exaggerated in undernutrition. They carried out no experiments on normal people and may not even have been aware of the large amount of earlier work which had all indicated that effects very similar to the ones they were observing might be brought about by a change of posture in well-nourished individuals. Edel (1901), for example, Linossier and Lemoine (1903), Loeb (1905) and, more recently, Bull (1948) studied this matter out of interest in postural albuminuria, and Seyderhelm and Goldberg (1926), White, Rosen, Fischer and Wood (1926), Ni and Rehberg (1931), Asmussen, Christensen and Nielsen (1938) and McCann and Romansky (1940a,b), did the same from an interest in fluid metabolism and the effects of gravity on vascular haemodynamics. Erlanger and Hooker (1904) overcame the effects of gravity in the erect attitude by immersing their subjects in a tank of water. Asmussen *et. al.* used a similar device, and others have bandaged the legs (Theobald, 1946). Ni and Rehberg took exogenous creatinine clearances as a guide to the glomerular filtration rate, and most of the modern studies have been made with both inulin and diodone or *p*-aminohippuric acid in the circulation. The early investigators allowed their subjects some movement in the erect

attitude, but some of the recent workers have used tilting tables to minimize movement and muscular action.

It is quite clear from all this work that the erect attitude reduces the output of water. Linossier and Lemoine (1903), Erlanger and Hooker (1904), Loeb (1905), White *et. al.* (1926) and Bull (1948) found that the output of NaCl was also reduced, but not to the same extent, and Seyderhelm and Goldberg (1926) showed that this was also true when saline was used as a diuretic. Brun, Knudsen and Raaschou (1945a,b) found a small but inconsistent fall in the inulin clearance and a rather larger fall in the diodone clearance in the passive erect attitude, and Bull (1948) confirmed this in youths standing in a position of lordosis. Recent work has tended to show that the inulin clearance is less reduced by the erect attitude than the excretion of water, and that the inulin/diodone clearance ratios tend to be raised. While, therefore, a change of posture may affect the haemodynamics of the kidney, the fall in the output of water in the erect attitude must be attributed mainly to an increased reabsorption of water (Brun *et al.* 1945a).

Practically all these studies have been made after the administration of water to the subjects, but Brun *et al.* (1945a) stated that the excretion of water was similarly affected by posture in subjects who had had no fluid by mouth for 12 to 18 hours.

The present investigations have covered several aspects of renal function which will be described separately. All the chemical methods which were used are described in the Appendix (p. 401).

Part 1

THE EXCRETION OF WATER AFTER A TEST DOSE

Subjects and Methods

The tests on the undernourished men were all made during July and August 1946, at the Städtisches Krankenhaus, Wuppertal-Barmen. The controls were convalescent men of similar age at White Lodge Hospital, Newmarket, and Addenbrooke's Hospital, Cambridge. The tests at Newmarket were made in July 1947, those at Addenbrooke's Hospital in April 1948. Table 1 gives the ages, complications, if any, and the degree of oedema, if any, of the undernourished men, and also the ages of the controls and the illnesses from which they had been suffering. All the undernourished men had lost a considerable amount of weight and had other characteristic signs of undernutrition.

The tests occupied two days: on one the subject got up as usual at about 6 a.m. and remained up and about until the end of the test, and on the other he remained recumbent in bed. Recumbent patients were not allowed to sit up, and the patients who were up and about were allowed to be seated only for meals. They took no strenuous exercise, but stood or pottered about the wards. Half of the subjects were recumbent on the first day, the other half on the second day. In all other respects the procedure was exactly the same on both days, and was as follows:

At 8 a.m. the subject emptied his bladder, and the urine was discarded. At 8.30 a.m. he had breakfast consisting, in the case of the German subjects, of three slices of bread and jam and one small cup of "Ersatz" coffee, and, in the case of English patients, of two slices of bread and butter, one small cup of tea, and egg, bacon or sausage according to the day's menu. At 11 a.m. the bladder was

TABLE 1

Description of subjects

Undernourished subjects				Controls	
Subject	Age	Oedema grading on admission	Complications	Age	Illness
B 5	54	1		62	Arthrodesis of hip
B 8	62	3		47	Bronchiectasis
B 9	60	2		50	Convalescent pulmonary T.B.
B 26	26	4		55	" " "
B 33	25	0		38	Anxiety state
B 34	40	4		58	Knee operation
B 35	49	0		20	Epileptic
B 36	50	0		75	Carcinoma of ear
B 37	64	4		30	Anxiety state
B 40	43	4		26	" "
B 42	54	2			
B 43	48	1	Osteomyelitis Myocardial degeneration		
B 44	44	2			
B 45	69	2	Hypertension		
B 46	49	2			
B 47	41	2			
B 48	62	2			
B 49	57	2			
B 50	44	2			
B 52	54	0			
B 59	52	2			

TABLE 2

Average minute volumes of the urine of well-nourished and undernourished men in the recumbent and erect attitudes after taking 1,200 *c.c. water*

Time after taking water (min.)	Volume of urine (c.c./min.)			
	Undernourished men		Well-nourished men	
	Recumbent	Erect	Recumbent	Erect
0–30	1·6	1·4	2·7	1·2
30–60	4·1	2·7	7·5	3·7
60–90	9·4	6·0	10·8	7·9
90–120	9·0	5·1	7·4	5·3
120–180	2·7	2·3	2·9	2·2
180–240	1·7	1·2	1·4	1·0
240–300	1·2	0·7	1·2	0·9
Total output in 5 hours (c.c.)	1,052	698	1,184	794

again emptied and the volume measured and recorded, and the subject was then immediately given 1,200 c.c. of water flavoured with lemonade. It took five to ten minutes to drink this. Urine was collected and measured at 11.30 a.m. and thereafter at half-hourly intervals until 1 p.m., when the midday meal was

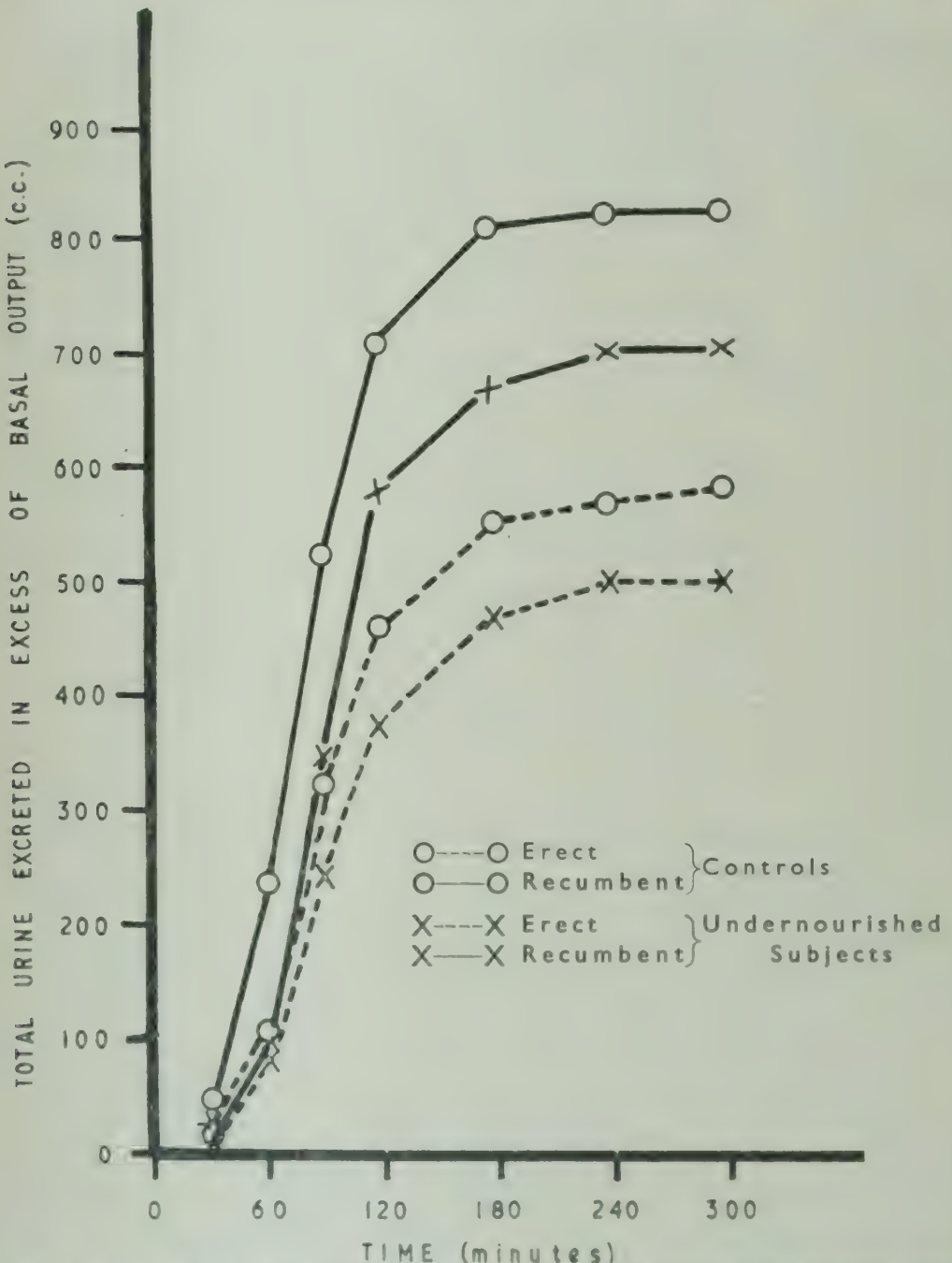

Fig. 1. Total volumes of urine excreted in excess of "basal" output after drinking 1,200 c.c. of water

taken. Watery vegetables and soup were excluded from this meal and the subjects had nothing to drink with it or after it. From the figures obtained the rate of excretion during each collecting period, the total volume excreted between 11 a.m. and 4 p.m., and the total volume excreted during this time over and above the "basal" rate were calculated. The basal values were taken to be the

rates of excretion after the diuretic effects of the water had subsided and were 1·2 c.c. per min. in the recumbent and 0·7 c.c. per min. in the erect attitude (see Table 2).

Results

Table 2 shows the average volumes of urine produced per minute during each collecting period, and also the total volumes passed between 11 a.m. and 4 p.m. Fig. 1 shows the total volumes produced over and above the basal output by the end of each collecting period, plotted against time. There are several comparisons to be made. If, firstly, the total volumes passed by the well-nourished and undernourished men are studied (*a*) in the recumbent (*b*) in the erect attitudes, it will be seen that in each attitude the volumes produced by the undernourished were somewhat smaller. These differences would have been a little less if the two undernourished men with complications likely to affect the urine volumes had been excluded from the series, but in any case they were not statistically significant when each attitude was considered separately (recumbent: $t = 1{\cdot}293$, $P = 0{\cdot}3$–$0{\cdot}2$; erect: $t = 0{\cdot}857$, $P = 0{\cdot}4$–$0{\cdot}3$), or when the volumes in both attitudes were taken together ($t = 1{\cdot}285$, $P = 0{\cdot}2$–$0{\cdot}1$). It will also be seen from Table 2 and Fig. 1 that the time of onset and general characteristics of the diuresis were unaffected by undernutrition. These results, therefore, confirmed those of Schittenhelm and Schlecht (1918, 1919) and of others who have studied this subject. They should probably not be taken, without further evidence, as a contradiction of Schwarz's (1945) results, for his subjects appear to have been much more undernourished. It will next be seen that the present results have demonstrated effects of posture on the urine flow of well-nourished men similar to those which have been described many times before. The difference between the two attitudes was statistically significant ($t = 2{\cdot}881$, $P = 0{\cdot}02$–$0{\cdot}01$) and the ratio of the total volume passed recumbent/the volume passed erect was 1·50. Finally it will be noted that posture had a very similar effect upon the urine flow of undernourished men. The difference between the two averages was again statistically significant ($t = 4{\cdot}668$, $P = 0{\cdot}01$). The ratio of the total volume passed recumbent/volume passed erect was 1·51, which is almost exactly the same as the ratio obtained for the well-nourished men. It may be concluded, therefore, that, following a test dose of water, gravity had no *more* effect on the urine flow of undernourished men than it had on the urine flow of well-nourished men.

Part 2

THE EFFECT OF POSTURE ON THE EXCRETION OF WATER, INULIN, DIODONE, UREA AND CHLORIDES AFTER THE ADMINISTRATION OF WATER

Subjects and Methods

The main experiments were carried out on 11 undernourished men in Wuppertal in the summer of 1946. Their ages ranged from 26 to 54. Three had been prisoners of war in Russian hands and the rest were members of the civilian population. One man was slightly overweight, but he had a considerable amount of oedema. The other ten all weighed less than would have been expected from their heights and ages according to the Hassing-Schall standards, and they were on the average 14 per cent underweight (range 4–33 per cent).

All of them had or had had oedema, and all of them had been admitted to hospital for one or other of the nutritional investigations.

The tests were made on two, usually but not necessarily, consecutive days. Half the men were first tested in the recumbent position and the other half in the erect position. On days when tests in the erect attitude were to be made the men got up before breakfast and remained up and about, standing as much as possible, till the tests were completed. During the actual tests the men stood propped up against a table almost without movement, and the infusions were given into one arm, which rested on a support covered with a mackintosh pillow so adjusted that the forearm was horizontal. On days set aside for tests in the recumbent attitude the men were kept in bed until the last experimental urine had been collected. The air temperature could not be controlled, but did not vary much from day to day and it was in general a cool summer. The men were kept comfortably warm during the test days whether or not they were in bed.

The experimental routine was as follows: after an overnight fast breakfast (bread and jam, but no fluid) was taken at 8.30 a.m. At 10 a.m. the man emptied his bladder and this urine was thrown away. At noon he again emptied his bladder, standing up for a moment to do so if he wished. This urine was collected, measured and used for the concentration tests described later in Part 3. At 12.15 p.m. the subject took his lunch which consisted of 500 c.c. of thick soup. At 2.15 p.m. the subject emptied his bladder once more and then drank 1,300 c.c. of water. Urine was collected and measured at 2.45 and often at 3.15 p.m. At about 3.10 p.m. a needle or a small trocar and cannula was inserted into one of the veins in the antecubital fossa or forearm, and a priming solution of inulin and diodone was given over a period of 3 or 4 minutes. This consisted of 3 c.c. of 30 per cent "Perabrodil" and 4·5 g. of inulin in 37 c.c. of 0·9 per cent saline. The syringe which had contained the priming solution was at once disconnected from the needle or cannula and replaced by another which contained the maintenance solution. This was given at the rate of 0·5 c.c. per minute, and each 100 c.c. contained 8 g. of inulin, 12 c.c. of 30 per cent "Perabrodil" and 88 c.c. of 0·9 per cent saline. The man emptied his bladder again about 70 minutes after taking the water and the exact time was noted. Ten minutes later a specimen of blood was taken from the arm which was not being used for the infusions and two further specimens of urine were collected, accurately timed and measured at approximately 20-minute intervals. A second specimen of blood was taken about 20 minutes after the first, i.e. at the mid-point of the second experimental period which terminated about 115 minutes after taking the water. Thereafter urines were collected less frequently until the diuresis had subsided.

By adopting this experimental time-table the urine collected after the first sample of blood nearly always covered the peak of the diuresis, and the minute volume of the next specimen of urine was generally just a little lower but of very much the same order of magnitude. Thereafter the flow of urine subsided more or less rapidly, and only the two urines covered by the samples of blood were analysed for inulin and diodone, and the infusions were discontinued after these specimens had been collected. The intervals of time during which these two specimens of urine were formed will be referred to as periods 1 and 2. Catheters were not used, and only one man had the slightest difficulty in emptying his bladder at the appointed time. In five of the men the blood pressure was taken once or twice during each test. Blood for analysis was withdrawn with a minimum

of stasis and placed under paraffin. It was allowed to clot, the corpuscles were separated as quickly as possible, and the serum used for all determinations. Urines were preserved for analytical purposes with toluene.

Results

Table 3 shows the effect of posture upon the blood pressure, the minute volume of the urine, the inulin clearance (i.e. the glomerular filtration rate), the minute volume × 100/inulin clearance (i.e. the percentage of the water in the glomerular filtrate to be excreted), the diodone clearance (or renal plasma flow), the inulin clearance × 100/diodone clearance (the so-called filtration fraction), and the urea clearance (calculated as UV/P). The figures shown were obtained by adding together the results of each of these determinations or calculations in periods 1 and 2 (*vide supra*) and dividing the answer by 2.

TABLE 3

Effect of posture on the blood pressure, minute volume, clearances and clearance ratios

Subject and No.	Erect or recumbent	B.P. (mm. Hg)	Minute volume (c.c.)	Inulin clearance (c.c./min.)	Min. vol. × 100/ Inulin clearance	Diodone clearance (c.c./min.)	Inulin clearance × 100/ Diodone clearance	Urea clearance (c.c./min.)
Brec.	R	108/80	13·5	123	10·9	411	30·2	94·2
(B 107)	E	150/100	1·3	116	1·1	420	27·7	31·6
Wolf.	R	118/75	9·7	115	8·3	646	18·0	101·1
(B 104)	E	102/76	3·8	126	2·9	588	21·5	34·4
Wesk.	R	—	12·3	111	11·1	442	25·1	73·5
(B 1)	E	110/70	5·7	120	4·7	478	25·0	52·2
Neph.	R	110/60	14·0	146	9·5	610	24·4	111·2
(B 128)	E	110/75	0·9	107	0·8	455	23·7	13·1
Schl.	R	—	12·5	130	9·7	493	26·3	76·9
(B 100)	E	—	0·6	85	0·7	303	27·9	11·7
Beck.	R	—	4·1	134	3·0	636	21·0	63·9
(B 26)	E	—	1·7	50	3·4	308	16·6	29·3
Figg.	R	132/75	12·7	107	11·9	591	18·5	62·5
(B 93)	E	115/75	3·5	111	3·1	538	20·6	25·5
Kuhn.	R	—	11·8	93	12·7	460	20·4	83·0
(B 88)	E	—	5·9	73	8·0	331	22·2	56·2
Lang.	R	120/75	10·4	120	8·7	468	25·5	83·3
(B 116)	E	135/80	9·6	124	7·6	466	26·6	77·2
Greb.	R	—	10·2	117	8·7	521	22·4	—
(B 74)	E	—	0·5	115	0·4	613	18·9	10·3
	E	—	2·4	104	2·4	519	20·5	76·0
Schm.	R	—	10·2	117	8·7	521	22·4	—
(B 36)	E	—	7·0	94	7·5	515	18·3	—

The findings may be summarized thus: (1) The blood pressure was sometimes higher and sometimes lower when the men were standing up, and it is impossible to correlate any of the changes in renal function with variations in it. (2) The

adoption of the erect attitude produced without exception a fall, and sometimes a very large fall, in the minute volume. Brec., Schl., Neph. and Greb. were most affected. In Brec., for instance, the minute volume standing up was only about a tenth of its value in the recumbent attitude and in Schl. and Neph. it was an even smaller proportion. (3) A change to the erect attitude produced either no significant change or a relatively small fall in the glomerular filtration rate. The fall was greatest in the experiments on Beck., in whom the fall in minute volume was relatively slight. A large fall in minute volume was not necessarily associated with a fall in the inulin clearance, although both did fall together in Brec., Schl. and Neph. (4) Although these experiments were not carried out in quite the same way, the results in general are a confirmation of those of Brun *et al.* (1945a, b) and of Bull (1948). They show that the fall in minute volume occasioned by the assumption of the erect attitude was mainly caused by the increased percentage of water reabsorbed from the glomerular filtrates. Only in Beck was this percentage the same in both attitudes, so that only in this man can the fall in glomerular filtration rate be held to account for the fall in the minute volume. (5) The diodone clearance, like the inulin clearance, was relatively little affected by a change of posture, and the two did not always move together. They did so, however, in the experiments on Neph. and Schl., and particularly in those on Beck. (6) A change of posture had no consistent effect upon the filtration fraction, but (7) the urea clearance was greatly reduced by the erect attitude. In some men this was particularly evident in period 2 when the minute volumes were just beginning to fall. Some examples of this are given in Table 4. It will be seen that the fall in the urea clearance was sometimes greater than the fall in the minute volume, and produced a great change in the urea/inulin clearance ratio. Although in some men, as Table 4 shows, an equally great change in minute

TABLE 4

Effect of a fall in minute volume on the urea clearance and the urea/inulin clearance ratio in the erect attitude

Subject	Minute volume (c.c.)		Inulin clearance (c.c./min.)		Urea clearance (c.c./min.)		Urea/inulin clearance ratio	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Wolf.	5·25	2·27	130	122	50·7	18·2	0·39	0·15
Schl.	0·70	0·50	85	84	15·4	8·0	0·18	0·09
Neph.	1·38	0·41	113	101	18·0	8·1	0·16	0·08
Beck.	1·91	1·52	56	44	28·7	30·0	0·51	0·68
Greb.	0·43	0·50	110	121	7·5	13·2	0·07	0·11
	3·13	1·70	95	113	78·4	73·7	0·82	0·65

volume did not affect the urea clearances, a dramatic fall in the urea clearance was most conspicuous in men whose minute volumes in period 2 were considerably lower than they were in period 1. These falls in urea clearance when the minute volumes begin to fall clearly require consideration in any discussion of the way in which urea is excreted and reabsorbed (see later). They appear to be the converse of the sudden rise in the urea clearances and urea creatinine clearance ratios when the minute volumes begin to increase, which was first observed by Shannon (1936) in experiments on the dog.

The chlorides were determined in the serum and urines of nine men and in most of these urines the freezing-points were also measured. It is possible, therefore, to analyse the effects of posture on these men a little further. Table 5 shows the composition of their urines. As data for freezing-points are given

TABLE 5

Effect of posture on the minute volumes, freezing-points, and urea and chloride concentrations of urines after drinking 1,300 *c.c. water*

Subject	Recumbent				Erect			
	Min. vol. (c.c.)	F.P. (m. mol./l.)	Urine Cl (2 × m. equiv./l.)	Urine urea (m. mol./l.)	Min. vol. (c.c.)	F.P. (m. mol./l.)	Urine Cl (2 × m. equiv./l.)	Urine urea (m. mol./l.)
Brec.	13·5	118	41	23	1·3	810	486	92
Wolf.	9·7	183	84	49	3·8	231	108	40
Wesk.	12·3	167	55	45	5·7	194	109	70
Neph.	14·0	83	29	34	0·9	465	258	74
Schl.	12·5	145	63	43	0·6	590	287	134
Beck.	4·1	462	259	82	1·7	301	128	87
Figg.	12·7	135	58	30	3·5	258	89	44
Kuhn.	11·8	151	75	40	5·9	134	38	54
Lang.	10·4	151	71	48	9·6	140	48	49
Average	11·2	177	82	44	3·7	347	172	72

in this Table, the chlorides have been expressed as 2 × m. equiv. per litre to give an approximation to the osmotic pressure for which they are likely to have been responsible, and it will be noted that a fall in minute volume was generally accompanied by a rise in the concentration of chlorides and urea and in the total osmotic pressure of the urines. The fall, however, made curiously little difference to the freezing points in some instances, and surprisingly little change in the concentrations of chlorides and urea. It must be remembered that these experiments were not strictly controlled, in that the subjects were not tested in both attitudes on the same day and the intakes of food and salt were not carefully regulated. It is simplest, for example, to explain Kuhn.'s urinary chlorides as due to a change of intake. If, however, the figures in Tables 3 and 5 are considered together, it may be calculated that in all the men except Beck. the assumption of the erect attitude led to the reabsorption of more chlorides and urea from the glomerular filtrates. The average figures are given in Table 6.

TABLE 6

Average percentages of water, chlorides and urea reabsorbed from the glomerular filtrates

Posture	Water		Chlorides		Urea	
	Average percentage	Standard deviation	Average percentage	Standard deviation	Average percentage	Standard deviation
Recumbent	89·6	1·5	97·1	0·8	25·9	10·1
Erect ..	96·3	2·9	98·5	0·5	64·3	23·4

The reabsorption of urea varied very much from one subject to another and from one posture to another. Neph. and Schl. reabsorbed over 90 per cent of the urea in their glomerular filtrates during the second period when they were standing, and Kuhn. only 6·6 per cent when he was recumbent in period 1. He and Wolf. reabsorbed only some 10 per cent of their urea in the recumbent position over the two periods taken together. The results as a whole confirm the findings of others (*vide supra*) that the assumption of the erect attitude reduces the output of chlorides and urea, but not to the same extent as that of water. Thus, the average rates of excretion of water, chlorides and urea in the erect attitude were respectively 32·3, 49·1 and 47·5 per cent of the rates in the recumbent attitude.

Since no significant differences had been found between the responses of undernourished and normal men to a test dose of water, and since the observations made after the administration of inulin and diodone to undernourished men so much resembled those which had been made by others on normal persons, it was decided not to carry out a series of tests similar to the above on well-nourished men.

Part 3

THE EXCRETION OF WATER, CHLORIDES AND UREA BY UNDERNOURISHED MEN AFTER 16 HOURS WITHOUT FLUIDS

Subjects and Methods

The 11 men who were described in Part 2 were also the subjects for these experiments. The urines were collected between 10 a.m. and noon as described in Part 2, measured, and preserved under toluene.

TABLE 7

Effect of posture on the minute volumes, freezing-points, and urea and chloride concentrations of urines after a period of 16 *hours without water*

Subject	Recumbent				Erect			
	Min. vol. (c.c.)	F.P. (m. osmol. per l.)	Urine Cl (2 × m. equiv./l.)	Urine urea (m. osmol. per l.)	Min. vol. (c.c.)	F.P. (m. osmol. per l.)	Urine Cl (2 × m. equiv./l.)	Urine urea (m. osmol. per l.)
Brec.	1·2	511	336	97	0·7	629	481	75
Wolf.	3·3	549	326	79	1·0	721	545	80
Wesk.	1·4	909	491	228	0·7	1,081	608	302
Neph.	1·6	630	313	89	0·1	—	255	75
Schl.	0·8	823	515	208	0·5	861	575	156
Beck.	3·2	—	440	—	0·8	801	422	—
Figg.	1·5	866	516	229	0·8	908	468	244
Kuhn.	1·6	538	335	146	0·3	834	448	151
Lang.	2·0	844	534	177	0·9	904	543	213
Greb.	1·7	158	373	—	0·5	1,032	493	—
Average	1·8	714	438	157	0·6	863	484	162

Results

The minute volumes, freezing-points (expressed as m. osmol./litre) and the concentrations of chloride and of urea are shown in Table 7. The osmotic pressures and the urinary concentrations tended naturally to be much higher than they were after taking the water (Table 5), but Neph. and Schl. had such small minute volumes in the erect attitude, even after taking the water, that the differences in them were small. It will be noted that even after a period of 16 hours without fluids the minute volumes were always greater when the subjects were recumbent and sometimes considerably so. The osmotic pressures of the urines were lower in the recumbent attitude as were the concentrations of chlorides in nearly all the men, but in spite of this the rate of excretion of chloride was on the whole greater when the subjects were recumbent. In other words, the erect attitude again reduced the rate of excretion of water to a greater extent than that of chlorides. The concentrations of urea were curiously little affected by posture but the rate of excretion was always greater in the recumbent than in the erect attitude. The average rates of excretion of water, chlorides and urea in the erect attitudes were respectively 37·3, 45·1 and 44·5 per cent of their values in the recumbent attitude.

The value of these experiments lies in the fact that they were made on the same men as those on whom the experiments with inulin and diodone were carried out after large draughts of water. They serve, therefore, to bridge the gap between the experiments described in Part 2 and those about to be reported in Part 4.

Part 4

THE EFFECT OF UNDERNUTRITION AND OF POSTURE ON THE OSMOTIC PRESSURE OF THE URINE AND ON THE EXCRETION OF WATER, CHLORIDES AND UREA AFTER 16 HOURS WITHOUT FLUIDS, AND THE EFFECT OF THE PITUITARY HORMONE ON THESE FUNCTIONS

Subjects and Methods

There were four groups of subjects for these experiments:

1. Twenty-one undernourished men who had been sent to the clinic in July 1946 on account of their oedema and on whom a concentration test was made while they were in hospital for other investigations. The men were up and about the ward during the test, but posture was not strictly controlled. They were 68 to 115 per cent (average 89 per cent) of their standard weights. Their ages ranged from 25 to 69, but only two were under 40 and the average age was 49. All of them had or had had oedema, but the subjects were not selected in any other way. The tests on these men were carried out as described in Part 2.

2. Thirty-two young and middle-aged civilian prisoners in Siegburg gaol. This group was selected in the following way: In the summer of 1946, the most undernourished prisoners were asked if they would volunteer for some tests, and a preliminary "concentration" test was carried out on 64 of them in the erect attitude. This was intended as practice for the men and prison staff and it was known that only 32 could be taken for the main experiments. Some of the men had difficulty in emptying their bladders to order, and others passed inexplicably large volumes of urine; three, for example, had volumes which exceeded 2 c.c. per minute. Only three produced urines with osmotic pressures

which exceeded 1,100 m. osmol. per litre and it seemed clear enough at the time that the men as a whole were not producing "normal" urine concentrations. With the idea, therefore, of getting a more homogeneous group on whom to study the effects of posture on the formation of urine, the men who had difficulty in emptying their bladders were discarded. Nine men with the largest minute volumes and 12 with the highest urinary osmotic pressures were also excluded from further studies, and the remaining 32 were used for the comparative experiments. These men were all much underweight, but only a proportion of them had oedema. Their ages ranged from 22 to 58 and averaged 36 years.

3. A group of 20 young and middle-aged civilians at Siegburg gaol who were selected in July 1947 on account of their undernutrition. Their ages ranged from 21 to 59 but half of them were 30 or below. They were in a much better state of health than the men who had been tested the year before, but they were only 72 to 89 per cent (average 80 per cent) of their standard weights. Few of these men had oedema at the time of the tests.

4. A group of 24 healthy well-nourished Germans who had been prisoners of war and who were working as farm labourers near Cambridge, England. Their ages ranged from 20 to 42 years with an average of 29, which made them a good series with which to compare the Siegburg men. Their food had been amply sufficient both in quality and quantity. For some of the comparisons the results of tests on four British soldiers were available and have been included.

The experiments at Siegburg in 1946 were carried out in the following way: The men took their usual evening meal at 5 p.m. on the day before the tests and went to bed at 7 p.m. They got up at 6 a.m. and went to a large communal cell where they were given only bread for breakfast. At 9.30 all emptied their bladders, and this urine was thrown away. At 11.10 the men again emptied their bladders into numbered cylinders, and this urine was saved for analysis. The men were divided into four groups of eight and tests were made on the Tuesdays and Saturdays of two consecutive weeks. The men in one group lay down at 6.30 a.m. and remained recumbent, except when they rose to empty their bladders, till the test was over. The men in the other three groups stood about the cell. The men in one of these groups were given 4 g. of sodium chloride and 8 g. of urea in 40 c.c. of water at 6.30 a.m.; those in another group were given

TABLE 8

Effect of undernutrition and of posture on the minute volume, the osmotic pressure and the sodium chloride and urea concentrations in the urine

	Recumbent			Erect			
	Normal controls	Siegburg 1946	Siegburg 1947	Normal controls	Siegburg 1946	Siegburg 1947	Clinic patients
Minute volume (c.c.)	1·38	2·45	1·53	0·62	0·65	0·93	0·65
Osmotic pressure (m. osmol./l.)	807	580	670	1,034	780	870	970
Chlorides (2 × m. equiv./l.)	418	363	440	523	440	558	325
Urea (m. mol./l.)	226	136	146	358	166	196	336

400 m. units of post-pituitary hormone at 9·30 a.m. Each group carried out a different test on each of the four experimental days, so that at the end all the 32 men had been subjected to each of the four tests.

The experiments at Siegburg in 1947 were carried out in exactly the same way, the 20 men being divided into three groups. In one the men lay down during the tests; in another the men lay down and were given 400 m. units of post-pituitary hormone; the men in the third group remained on their feet from 6.30 a.m. till the test was over.

TABLE 9

Statistical significance of results given in Table 8

Groups compared	Minute volume	Osmotic pressure	Chloride concentration	Urea concentration
Normal subjects recumbent and erect	Recumbent higher $t = 7{\cdot}08$, $P < 0{\cdot}01$	Recumbent lower $t = 5{\cdot}38$, $P < 0{\cdot}01$	Recumbent lower $t = 5{\cdot}1$, $P < 0{\cdot}01$	Recumbent lower $t = 7{\cdot}6$, $P < 0{\cdot}01$
Siegburg subjects (1946) recumbent and erect	Recumbent higher $t = 7{\cdot}53$, $P < 0{\cdot}01$	Recumbent lower $t = 6{\cdot}66$, $P < 0{\cdot}01$	Recumbent lower $t = 3{\cdot}1$, $P < 0{\cdot}01$	Recumbent lower $t = 2{\cdot}62$, $P < 0{\cdot}02 > 0{\cdot}01$
Siegburg subjects (1947) recumbent and erect	Recumbent higher $t = 3{\cdot}37$, $P < 0{\cdot}01$	Recumbent lower $t = 5{\cdot}86$, $P < 0{\cdot}01$	Recumbent lower $t = 4{\cdot}01$, $P < 0{\cdot}01$	Recumbent lower $t = 2{\cdot}62$, $P < 0{\cdot}02 > 0{\cdot}01$
Normal subjects and Siegburg subjects (1946) recumbent	Siegburg higher $t = 4{\cdot}02$, $P < 0{\cdot}01$	Siegburg lower $t = 5{\cdot}48$, $P < 0{\cdot}01$	Difference not statistically significant	Siegburg lower $t = 5{\cdot}9$, $P < 0{\cdot}01$
Normal subjects and Siegburg subjects (1947) recumbent	Difference not statistically significant	Siegburg lower $t = 2{\cdot}48$, $P < 0{\cdot}05 > 0{\cdot}02$	Difference not statistically significant	Siegburg lower $t = 4{\cdot}22$, $P < 0{\cdot}01$
Normal subjects and Siegburg subjects (1946) erect	Difference not statistically significant	Siegburg lower $t = 8{\cdot}5$, $P < 0{\cdot}01$	Siegburg lower $t = 3{\cdot}18$, $P < 0{\cdot}01$	Sieburg lower $t = 14{\cdot}1$, $P < 0{\cdot}01$
Normal subjects and Siegburg subjects (1947) erect	Siegburg higher $t = 2{\cdot}88$, $P = 0{\cdot}01$	Siegburg lower $t = 3{\cdot}86$, $P < 0{\cdot}01$	Difference not statistically significant	Siegburg lower $t = 7{\cdot}76$, $P < 0{\cdot}01$
Normal subjects and clinic patients erect	Difference not statistically significant	Difference not statistically significant	Clinic patients lower $t = 5{\cdot}95$, $P < 0{\cdot}01$	Difference not statistically significant

The experiments on the normal controls at Cambridge were made in very much the same way, but there were minor differences in meal hours. There were three groups. The men in one remained on their feet, those in another remained on their feet and were given 4 g. of sodium chloride and 8 g. of urea 3 hours before the test period began, and those in the third group lay down during the tests.

Results

Table 8 contains the average results for the normal controls, for the Siegburg prisoners in 1946 and 1947 in the recumbent and erect attitudes, and for the clinic men, standing. This last group was not studied in the supine position. There are two quite separate comparisons to be made.

1. *The erect and recumbent attitudes.* The results for all three groups that were tested in both positions show that the minute volumes were higher and that the osmotic pressures of the urine and the urinary concentrations of urea and sodium chloride were lower when subjects were lying down. Each difference was statistically significant (see Table 9) and there can be no doubt at all that alterations of posture bring about similar changes of renal function in all subjects whether they are healthy or undernourished, or whether they have taken a large draught of water beforehand or not (see above). Brun *et al.*(1945a) suggested that the results obtained by them in similar experiments were due to variations in the quantity of post-pituitary hormone in the circulation, but no experiments with the hormone were carried out. Tests of this kind were clearly required and have accordingly been made. The results are given in Table 10.

TABLE 10

Effect of 400 *m. units of posterior-pituitary hormone on the minute volume, the osmotic pressure and the concentrations of sodium chloride and urea in the urine formed in the recumbent and erect attitudes*

	Siegburg 1946		Siegburg 1947	
	Erect	Erect + pituitary hormone	Recumbent	Recumbent + pituitary hormone
Minute volume (c.c.)	0·65	0·57	1·53	1·12
Osmotic pressure (m. osmol./l.)	780	807	670	807
Chlorides (2 × m. equiv./l.)	440	436	440	548
Urea (m. mol./l.) ..	166	157	146	152

It will be seen that giving 400 m. units of hormone to undernourished men in the recumbent attitude reduced the minute volume of the urine even when they had been without water for 16 hours, and raised the osmotic pressure and the concentrations of chloride and urea. The differences in minute volume, osmotic pressure and the concentration of chloride were statistically significant ($t = 2{\cdot}91$, $P = < 0{\cdot}01$; $t = 3{\cdot}76$, $P = < 0{\cdot}01$; and $t = 4{\cdot}6$, $P = < 0{\cdot}01$ respectively). It looks, therefore, as though lying down had reduced the output of post-pituitary hormone, and hence the amount in the circulation, to a level which

did not evoke a maximum response from the kidneys of these men. The administration of 400 m. units of post-pituitary hormone to the 1946 Siegburg group in the erect attitude made little change in their urinary picture. At any rate none of the differences was statistically significant. This suggests that in the erect posture the kidneys may already have been fully under the influence of the hormone, but the results that were obtained after giving sodium chloride and urea (see below) indicate that this may not have been the case.

2. *Normal and undernourished subjects.* Table 8 also shows comparisons between the groups of normal and undernourished subjects in the two attitudes. One other group of 19 undernourished subjects has been investigated in the erect attitude. These men took part in the dietary experiment described by *Widdowson* (p. 313), and the results collected will be found there. It will be seen that in the erect posture the normal subjects had the smallest average minute volume, and the difference between it and the value for the Siegburg 1947 group was significant (Table 9). The normal subjects had the highest average osmotic pressure, and the differences between it and the osmotic pressures for both the Siegburg groups were significant. This higher osmotic pressure was largely due to higher concentrations of urea and/or sodium chloride, and the significance of all these separate differences may be found in Table 9. The findings for the recumbent attitude (Table 8) confirmed the results obtained for the erect attitude, and it is evident that there was a distinct tendency for the undernourished groups to have larger average minute volumes than the normal subjects and/or lower osmotic pressures.

TABLE 11

Effect of 8 *g. urea and* 4 *g. NaCl by mouth on the minute volume, osmotic pressure, and concentrations of sodium chloride and urea in the urine* (*erect attitude*)

	Normal controls		Siegburg 1946	
	Undosed	Dosed	Undosed	Dosed
Minute volume (c.c.)	0·60	0·95	0·65	0·75
Osmotic pressure (m. osmol./l.)	1060	1065	780	865
Chlorides (2 × m. equiv./l.)	542	574	440	438
Urea (m. mol./l.) ..	369	306	166	238

Table 11 shows the results which were obtained after the ingestion of 4 g. of sodium chloride and 8 g. of urea in 40 c.c. of water. Here again there are two comparisons to be made.

1. *Nature of the response by normal and undernourished subjects.* Previous work (McCance, 1945) had indicated that normal people under the full influence of post-pituitary hormone would respond to the ingestion of 4 g. of sodium chloride and 8 g. of urea by an increase of urine volume rather than by a rise in the osmotic pressure of the urine. It will be seen that this expectation was fulfilled by experiment, for after the urea and sodium chloride had been administered the average minute volume of the normal men was increased significantly ($t = 5{\cdot}73$, $P = <0{\cdot}01$), but the osmotic pressure of the urine was not

raised. When a similar experiment was carried out on the group of undernourished Siegburg prisoners in 1946 it was found that they reacted rather differently, for the average osmotic pressure of the urine rose significantly ($t = 5{\cdot}22$, $P = <0{\cdot}01$) owing to the increased concentrations of urea in it ($t = 5{\cdot}75$, $P = <0{\cdot}01$). This suggests that the kidneys of these men were not under the full influence of the post-pituitary hormone even in the erect attitude, for the hypertonic solution of salt must be presumed to have raised the osmotic pressure of the urine by acting through the osmo-receptors (Verney, 1946) and the posterior pituitary. It must be admitted, however (*vide supra*), that these men did not respond to 400 m. units of post-pituitary hormone.

2. *Composition of the urine of normal and undernourished subjects after taking the urea and chloride.* It will be seen that, although the osmotic pressure of the urine of the undernourished group was significantly raised by the sodium chloride and urea, it still remained significantly below the normal, as did the concentrations of sodium chloride and urea ($t = 6{\cdot}13$, $P = <0{\cdot}01$; $t = 6{\cdot}8$, $P = <0{\cdot}01$; $t = 3{\cdot}82$, $P = <0{\cdot}01$, respectively). The minute volume was also larger, but the difference was not significant.

DISCUSSION

The foregoing results may be discussed by attempting to answer three questions.

1. What are the changes in the haemodynamics and function of the kidney brought about by standing up? The most constant and characteristic change is undoubtedly the fall in urine volume with secondary changes in the osmotic pressure and in the concentrations of sodium chloride and urea. Previous work on the subject with fully hydrated men has been confirmed, and the evidence given in Parts 3 and 4 shows that the statement made above applies with equal force to men who have had no water for 16 hours. The results reported in the papers reviewed in the introduction and the evidence brought forward in Part 2 all indicate that the changes underlying this reduction in minute volume are complicated and may differ considerably from one person to another. In some people neither the glomerular filtration rate (inulin clearance) nor the diodone clearance may fall (Table 3), in others they may both fall to the same extent, while in others the fall in the diodone clearance may exceed that in the glomerular filtration rate. Important as these changes are, and sufficient occasionally in themselves to explain the fall in urine flow, the reduction is usually brought about by an increased reabsorption of water from the glomerular filtrates. It is natural to postulate that this in turn is due to an increased liberation of post-pituitary hormone, but it would probably prove nothing to inject hormone into men who were overhydrated, for a response would certainly be obtained whether the subjects were erect or recumbent, and it would be very difficult to interpret the findings. The present experiments, however (Part 4), have shown that the injection of 400 m. units of hormone will reproduce in recumbent men who have been 16 hours without water the effects of standing up.

2. Do the effects of posture differ in normal and in undernourished persons? The evidence submitted in Part 1 suggests that after a draught of water the effects of posture on the volume of the urine are the same whether subjects are healthy or undernourished. The work described in Part 4 shows that the same is true of men who have had no fluids for 16 hours. The assumption of the erect attitude decreased the minute volume, and raised the osmotic pressure and

concentrations of sodium chloride and urea to very much the same extent in all the subjects. The experiments with inulin and diodone (Part 2) were limited to undernourished subjects, but a comparison of the results with those obtained by other investigators for normal people suggested that comparisons between small groups were unlikely to bring out any significant differences. The work carried out in Wuppertal and Cambridge has not, therefore, encouraged the view that hunger oedema can be explained by supposing that undernourished people are liable to effects of posture which do not operate in normal men, or even that they are unduly susceptible to the changes in renal function normally brought about by changes of posture.

3. What differences, if any, can be demonstrated between the secretion of urine by normal and undernourished men? It was shown in Part 1 that the response to a draught of water was essentially the same whether men were healthy or undernourished. This had been demonstrated before. The experiments detailed in Part 4, however, showed that after 16 hours without water the minute volumes of the undernourished groups tended to be higher than those of the normal men, and the osmotic pressures lower. Many of the differences were statistically significant and they are supported by the results obtained in the dietary experiments (*Widdowson*, p. 313). These appear to be real differences, but there is no evidence that they originate in the kidney, or that they indicate any reduced power of renal concentration. The urine of a healthy kidney is an expression of the volume and composition of the serum and extracellular fluids, which act on the kidney through their influences on the posterior pituitary, the suprarenal cortex, and possibly other ductless glands. The volumes of the extracellular fluids are known to be above normal in people who are undernourished, and the differences in the volume and osmotic pressure of the urines, demonstrated in Part 4, may be the result. In other words, the differences observed may be the result of differences in the composition of the organism, and not in the function of the kidney. This is the attitude generally adopted towards the voluminous diuresis induced by the recumbent posture in undernourished subjects, but the investigations of Schwarz (1945) in men, and of Brull and Op de Beeck (1943), Dicker, Heller and Hewer (1946), Heller and Dicker (1947), Brull (1947) and Dicker (1948a,b) in animals, have indicated that the kidney itself may be at fault. Within the limited conditions of the present experiments it must be admitted that nothing has been found to indicate that undernutrition brings about any abnormality in the function of the kidney.

SUMMARY

1. After a draught of water undernourished persons produced a diuresis similar in volume and in time relationships to that of normal persons.

2. A change from the recumbent to the erect attitude produced changes in the inulin and diodone clearances, and in the volume and composition of the urine, which were similar in normal and undernourished persons.

3. The reduction in urine volume brought about by changing from the supine to the erect position was usually the result of an increased reabsorption of water, but more chlorides and urea were also reabsorbed from the glomerular filtrates. The effects were reproduced by an injection of 400 m. units of post-pituitary hormone.

4. In undernourished persons who had had no fluids for 16 hours the urines tended to be larger in volume and lower in osmotic pressure than those of

normal persons. There is no evidence that this was due to a renal abnormality and it is submitted that the cause was the abnormal volume and composition of the extracellular fluids acting on the kidney through the usual channels.

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XI. SEROLOGICAL RESPONSES TO ANTIGENIC STIMULI

by P. G. H. Gell

Surprisingly little work appears to have been published on the ability of undernourished persons to produce antibodies, in spite of a widespread clinical impression that mass starvation is an important factor in the causation of epidemics. Famine has so often been accompanied by overcrowding, breakdown of normal sanitary measures, mass movements of the population and general demoralization, that it has seldom been possible to define, by observation and analysis, the part played by undernutrition *per se* in the genesis of epidemics. Further difficulties are introduced by the possibility that different types of malnutrition might produce different effects, for the various vitamin deficiencies, protein starvation and generalized undernutrition may each affect the resistance of the body to disease in different ways and to different degrees.

It is reasonable to expect that resistance, in so far as it is mediated by antibodies, would deteriorate *pari passu* with any failure of protein synthesis. Several investigators, in particular Cannon and his co-workers, have published the results of animal experiments bearing on this question. Wissler, Woolridge, Steffee and Cannon (1946) found that rats on a protein-deficient diet are less able to produce antibodies than are animals on diets providing the same number of Calories and containing adequate protein. Richardson (1935) found that in rabbits, undernutrition, due to a shortage of Calories, depressed agglutinin production against a typhoid vaccine. Hartley (1943) reported that a moderate restriction of diet reduced the response of normal guinea-pigs to diphtheric formol toxoid. Hartley, Evans and Hartley (1943) found that this moderate degree of restriction had little if any effect on secondary antitoxin production by immunized guinea-pigs; but in later work Hartley and Hartley (1947) found that prolonged and severe undernutrition had a definitely deleterious effect even here. Kligler, Guggenheim and Henig (1945), in an investigation of the role of vitamin A in protection, suggested that a low food intake, and not the reduced vitamin level, was responsible for the lowered resistance of their test rats to *Salmonella typhimurium* infection. Wilson, Saslaw, Schwab, Woolpert and Doan (1943) found that undernourished monkeys were susceptible to infection, although their antibody production was not diminished. In an interesting study of *Nippostrongylus muris* infestation in rats, Donaldson and Otto (1946) brought evidence to show that, to a small degree, the initial resistance to infection and, to a much greater degree, the resistance to re-infection was depressed in protein-starved rats. The latter at least is certainly an immune reaction, although the actual mechanism of immunity to nematode parasites is still rather obscure. Ruchman (1946) found in mice that underfeeding depressed the antibody response to a Western Equine Encephalomyelitis vaccine, as judged by protection experiments. A shortage of the whole vitamin B complex caused a slight depression, though thiamine or riboflavin deficiency alone had no effect. The only single vitamin deficiency which has been convincingly shown to be associated with diminished immunity responses is lack of pyridoxine (vitamin B_6). Stoerck, Eisen and John (1947) found that moderate caloric reduction had no effect, and protein deficiency very little, on the resistance of rats, when compared with the large effect of pyridoxine deficiency. They suggested that this might be due to the participation of pyridoxine as a coenzyme

in globulin synthesis. In one human case, Krebs (1946) found that a failure of antibody production against T.A.B. vaccine was correlated with a low level of γ-globulin in the serum.

Most experimental work has been concerned with malnutrition due to deficiency of a specific protein and it is in this field that the most striking results are to be expected. A country such as Germany, where the deficiency has been essentially one of Calories, might not therefore be considered the most suitable place in which to demonstrate a relationship between undernutrition and immunity production. From the practical point of view, however, a deficiency of Calories is the type of undernutrition which has most often been the fate of European countries and which has been the forerunner of widespread epidemic diseases. It was decided, therefore, in the spring of 1946, to investigate the immune responses of undernourished human subjects in Germany. The increase of antibody in the serum as a result of antigenic stimulus is the most easily measurable immune response, and this was therefore selected as a criterion. In order to demonstrate differences that might well be small it was clearly desirable to provide the maximal stimulus consistent with an absence of risk, and, if possible, of discomfort. On the assumption that a combination of different antigens would supply a stimulus more intense than an equivalent amount of a single antigen, an idea supported by the work of Björneböe (1943) and others, it was decided to use a triple antigen containing a bacterium, a pure protein, and a type of erythrocyte. Since, however, it was hoped to measure both the primary and the secondary responses, and also to avoid the inhomogeneity within the groups that would have been introduced by variable previous exposure, antigens against which there might be a pre-existent natural or acquired immunity could not be used. No pathogen could therefore be used for the bacterium in the vaccine, and a strain of saprophytic vibrio originally isolated from pond water by Dr. R. Jackson was chosen. A formolized vaccine made from this organism provoked a satisfactory antibody response in volunteers in a small preliminary experiment carried out in England, but the batch of vaccine used in Germany unfortunately rarely gave rise to any agglutinins at all, and so the results with this antigen have not been included in the data which follow. Tobacco-mosaic virus was taken for the protein constituent, since it was known to be a good antigen and could be titrated by a simple serum dilution method. Natural antibodies against it were not found, and it proved, in fact, to be ideal for the purpose in hand. Preliminary tests were made with the erythrocytes of rats, rabbits, fowls, and guinea-pigs. Agglutinins against all of these were found at low dilutions of normal human serum, but least often against fowl red cells, and these were accordingly used.

SUBJECTS

The undernourished subjects were selected after a clinical examination, which was carried out by other members of the Unit. They were divided into two groups: (*a*) 25 civil prisoners in the gaol at Siegburg, and (*b*) 32 undernourished men and women attending Barmen municipal hospital for extra rations on account of hunger oedema. Sixteen normal healthy persons, who acted as controls, included British soldiers stationed in the Wuppertal area and members of the Unit.

METHODS

The composite antigen was made up for injection by the following method: Blood was taken aseptically from the heart of an adult cock (the same animal was used throughout) and diluted with citrate-saline. The corpuscles were spun down and washed with saline, and the suspension made up to its original volume. One volume of these fowl red cells (hereafter FRC) was added to two volumes of a solution (2·5 per cent in 0·5 per cent formol-saline) of tobacco-mosaic virus (hereafter TMV) and two volumes of the vibrio vaccine ($2{\cdot}5 \times 10^9$ organisms per c.c. in 0·3 per cent formol-saline, heated to destroy H-agglutinogens). Of this mixture 0·5 c.c. was injected, so that each dose given contained 0·1 c.c. of FRC, 5 mg. of TMV, and 5×10^8 organisms. The injection was given within a few hours of mixing. Tenderness and swelling often appeared in 24 hours, but had usually subsided in 48 hours; no systemic reactions were observed.

All the subjects were given two subcutaneous injections in the upper arm at an interval of three weeks. Blood was taken before the first injection, and weekly for five weeks afterwards; an extra sample was taken on the fourth day of the last week. Thus, seven specimens were taken from each subject. Sera were separated in the evening and titrated the next morning.

For titration the sera were diluted 1 in 2 with saline, and "doubling-up" dilutions were made as high as was necessary. Dilutions were made with an automatic pipette with a changeable delivery tube, delivering unit volume of 0·2 c.c. One volume of each of the various dilutions was put in a $2 \times \frac{3}{8}$ in. Wassermann tube, and inactivated by heating in a water-bath for 20 minutes at 55°C. After cooling, one volume of FRC was added, and the racks placed in the incubator at 37°C. with occasional shaking for half an hour, and then put overnight in the ice-chest. Agglutination was estimated visually after shaking up the sedimented cells; there was nearly always one tube showing partial agglutination, and the dilution in this tube was taken as the end-point.

The sera were not inactivated for the agglutination of the vibrio and TMV. One volume of each of the dilutions of the sera was added to one volume of the vibrio at $1{\cdot}25 \times 10^9$ per c.c. or of TMV at 0·025 per cent in Dreyer tubes. These were stirred, incubated in a water-bath at 50°C. for four hours, and placed in the ice-chest overnight. The agglutination of the TMV was extremely clear-cut and easy to read, a light floccule settling to the bottom of the tube. The highest dilution in which a definite floccule appeared was taken as the end-point. As has been said above, agglutinins against the vibrio only appeared in one or two sera.

RESULTS

Some of the results are shown graphically in Figs. 1 and 2, and the experimental data are summarized in Table 1, which records the number of subjects in each group reacting at a given end titre at each time of sampling. The antibody response increased with time, as shown by the greater number of reactions at higher dilutions towards the end of the experiment. In general, the percentage of undernourished subjects reacting at the higher dilutions was definitely smaller than that of the controls, and it would seem reasonable to ascribe this to the undernutrition itself. The significance of the differences between the groups is not, however, immediately evident from inspection of Table 1, so a statistical

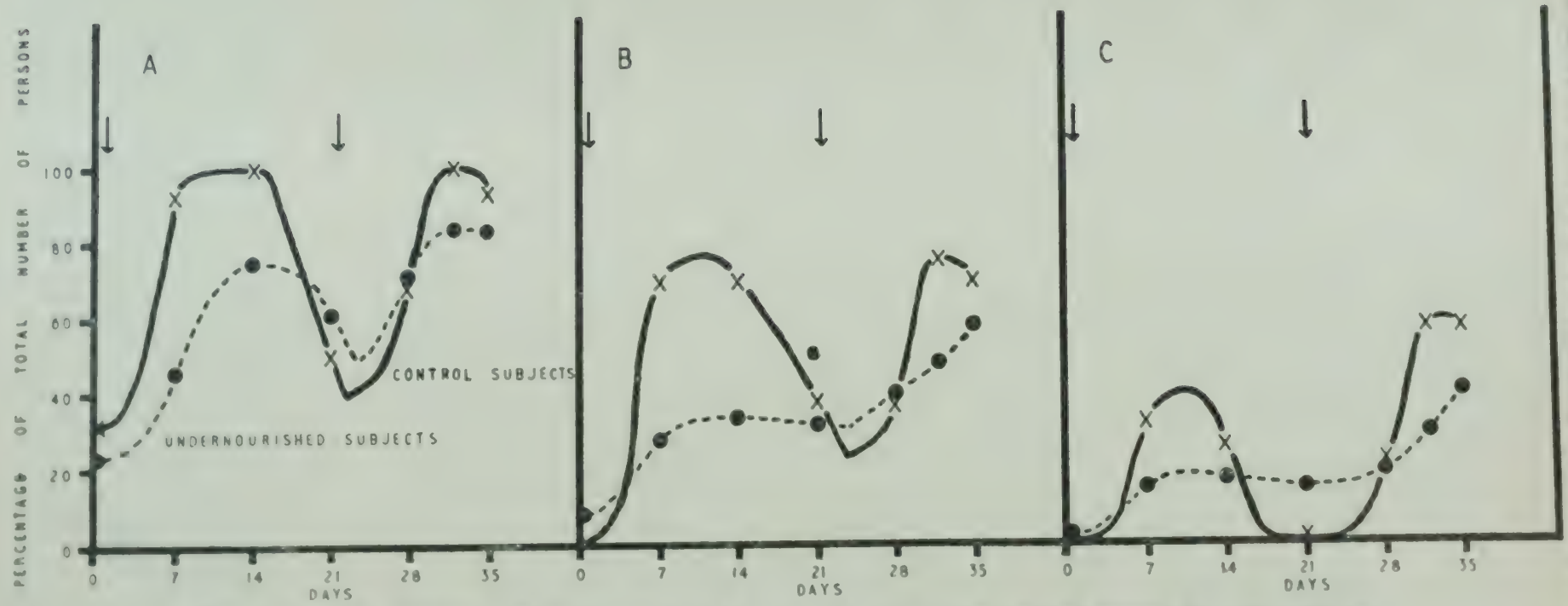

FIG. 1. Antibody responses of healthy controls (×—×—×) and undernourished persons (●----●----●) to fowl red cells. Diagram shows the percentage of persons in each group showing agglutination at (A) titres of $\frac{1}{4}$ and over, (B) titres of $\frac{1}{8}$ and over, (C) titres of $\frac{1}{16}$ and over, for each sampling period. Injections were given where indicated by the arrows.

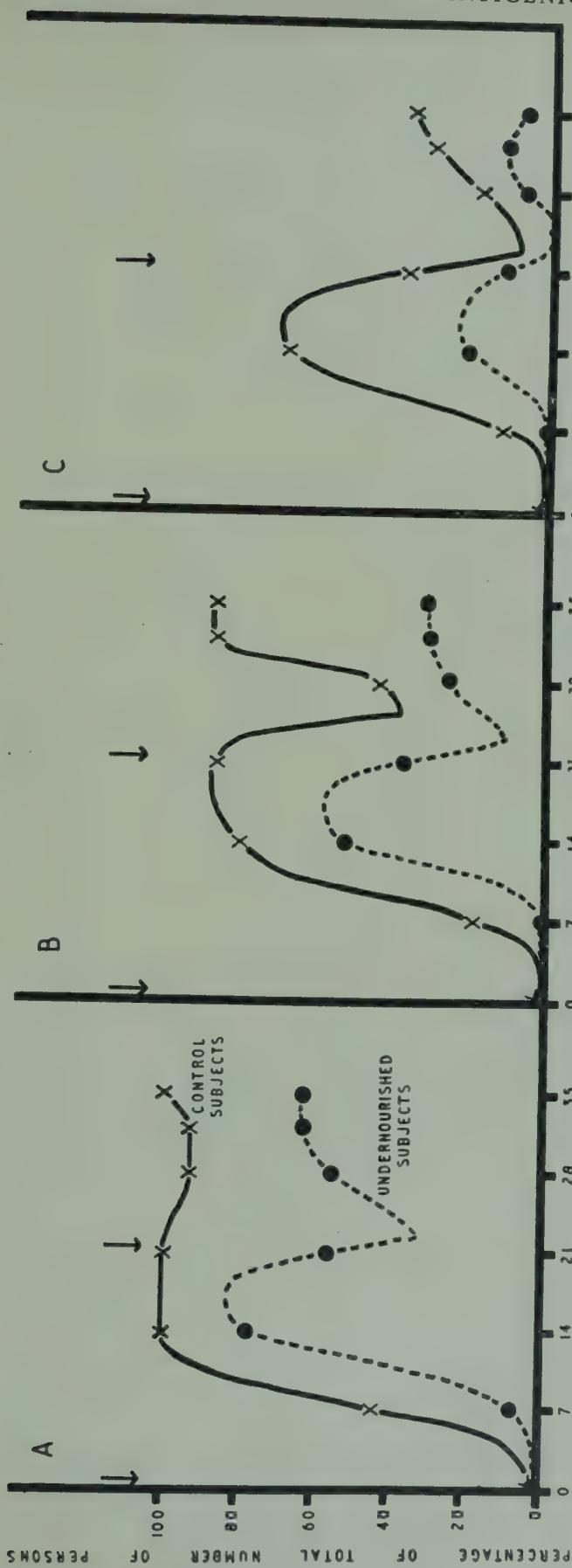

FIG. 2. Antibody responses of healthy controls (×—×—×) and undernourished persons (●---●---●) to tobacco-mosaic virus. Diagram shows the percentage of persons in each group with agglutination at (A) titres of $\frac{1}{4}$ and over, (B) titres of $\frac{1}{8}$ and over, (C) titres of $\frac{1}{16}$ and over, for each sampling period. Injections were given where indicated by the arrows.

TABLE 1

A summary of the immunity responses to fowl red cells and tobacco-mosaic virus

Antigen:		Fowl red cells							Tobacco-mosaic virus						
Sample:		I	II	III	IV	V	VI	VII	I	II	III	IV	V	VI	VII
Normal controls	No. of subjects reacting at titres of: <1/2	5	1	0	2	0	0	0	16	7	0	0	0	1	0
	1/2	6	0	0	6	5	0	1	0	2	0	0	1	0	0
	1/4	5	4	5	2	5	4	4	0	4	3	2	8	1	2
	1/8	0	6	7	6	3	3	2	0	1	2	8	4	9	8
	1/16	0	5	4	0	3	5	4	0	2	7	3	3	5	5
	>1/16	0	0	0	0	0	4	5	0	0	4	3	0	0	1
	No. in group	16	16	16	16	16	16	16	16	16	16	16	16	16	16
Siegburg prisoners	No. of subjects reacting at titres of: <1/2	13	5	1	5	0	2	0	25	23	1	3	3	2	2
	1/2	6	6	2	8	5	4	3	0	1	2	7	7	4	9
	1/4	4	6	9	5	9	5	9	0	1	9	5	8	9	5
	1/8	1	2	5	4	6	5	3	0	0	9	9	6	7	6
	1/16	1	4	7	2	4	7	7	0	0	3	1	1	3	2
	>1/16	0	2	1	1	1	2	2	0	0	1	0	0	0	0
	No. in group	25	25	25	25	25	25	24	25	25	25	25	25	25	24
Patients in Barmen Hospital	No. of subjects reacting at titres of: <1/2	18	10	1	2	2	0	4	32	25	8	10	6	6	5
	1/2	7	9	10	7	9	3	2	0	3	2	5	9	9	4
	1/4	5	5	15	12	9	16	5	0	3	5	6	9	10	12
	1/8	2	5	5	6	6	6	7	0	0	9	5	4	3	7
	1/16	0	2	0	4	3	6	10	0	0	4	4	2	4	1
	>1/16	0	0	1	1	2	1	2	0	0	4	2	1	0	1
	No. in group	32	31	32	32	31	32	30	32	31	32	32	31	32	30

Note. The figures represent the numbers agglutinating the FRC or TMV at the titre indicated in the left-hand column. Those reacting at over 1/16 are grouped together; these mostly reacted at titres of 1/32, and none at higher titres than 1/64. Concentrations of serum stronger [illegible] II, III, IV, V and VII were taken at weekly intervals after trials

analysis was kindly carried out by Dr. C. W. Emmens of the National Institute for Medical Research. For this purpose sampling periods (II, III, IV) were treated as one composite period, as were periods (V, VI, VII). An agglutination titre of $\frac{1}{4}$ represents about the most sensitive point on the scale for either FRC or TMV, and the percentages of subjects whose titres exceeded this value either at the pre-injection test (I) or on any occasion in either of the composite periods (II, III, IV) and (V, VI, VII) were calculated. Each individual subject whose titre exceeded $\frac{1}{4}$ at any one time is included in these percentages, and the results for periods (II, III, IV) and (V, VI, VII) are therefore higher than would be derived from the figures in Table 1, which gives only overall numbers and does not indicate whether the subjects exceeding the titre in, say, period IV are the same persons who had exceeded it in period III.

Table 2 shows those percentages of persons with agglutination titres of over $\frac{1}{4}$.

TABLE 2

Percentage of persons with agglutination titres of over 1/4

Antigen	Group	Sampling periods		
		I	II, III, IV	V, VI, VII
Fowl red cells	Siegburg	8·0	60·0	60·0
	Barmen	6·3	37·5	65·6
	Controls	0·0	81·3	87·5
Tobacco-mosaic virus	Sieburg	0·0	52·0	48·0
	Barmen	0·0	53·1	31·3
	Controls	0·0	93·7	93·7

Statistical analysis

1. The variance of each percentage is $\frac{x\,(100-x)}{N}$, where x = percentage over $\frac{1}{4}$, and N is the number of subjects in the group. (It may seem that, for strict comparability between sampling times, subjects should have been given three chances to exceed a titre of $\frac{1}{4}$ in period I instead of only one chance. The conclusions which follow are, however, based on comparison between groups and not between sampling times; thus, while the mean rises in the percentage with time may have been overestimated, all groups will have been equally affected and no bias occurs in making comparisons between them.)

2. A χ^2 test gives the following information about overall differences in response between the groups, P being the probability that the subjects in the groups are homogeneous:

	Sampling periods	χ^2	Degree of freedom	P
Fowl red cells	I	1·58	2	0·30–0·50
	II, III, IV	8·49	2	0·01–0·02
	V, VI, VII	2·87	2	0·20–0·30
Tobacco-mosaic virus	I	0·00	2	1·00
	II, III, IV	8·30	2	0·01–0·02
	V, VI, VII	15·49	2	$<$0·001

Only in period (II, III, IV) of the fowl red cell test was there a significant difference in response between the groups, whereas in the tobacco-mosaic test responses in both period (II, III, IV) and period (V, VI, VII) differ.

3. The most sensitive test of difference in response between groups is the difference in the mean percentage of subjects showing a rise in agglutination titre from period to period. In the tobacco-mosaic test the mean rises in titre above the values found in period I are identical with the absolute values. In the test with FRC the percentage showing a rise in titre is found

by taking the values in period I from those in periods (II, III, IV) and (V, VI, VII). In the table below *P* represents the chance that no difference exists:

	Groups	Responses	Difference/ Standard error	*P*
Fowl red cells	Control and Siegburg	(II, III, IV − I)	1·974	0·05–0·04
		(V, VI, VII − I)	2·550	0·02–0·01
	Control and Barmen	(II, III, IV − I)	3·668	< 0·001
		(V, VI, VII − I)	2·248	0·03–0·02
	Siegburg and Barmen	(II, III, IV − I)	1·392	0·17–0·16
		(V, VI, VII − I)	0·499	0·62–0·61

TAB

Correlation of antibody responses with ser

	Category 1 (no score)							Category 2 (score 1)						
	Subject number	Sex	Age	Serum protein (g./100 c.c.)	Serum albumen (g./100 c.c.)	Serum globulin (g./100 c.c.)	Percentage weight loss	Subject number	Sex	Age	Serum protein (g./100 c.c.)	Serum albumen (g./100 c.c.)	Serum globulin (g./100 c.c.)	Percentage
Patients in Barmen Hospital	B 4	M	65	5·7	3·8	1·9	+	B 1	M	41	6·5	4·4	2·1	
	B 9	M	60	5·8	3·7	2·1	25	B 2	F	63	6·3	3·9	2·4	
	B 10	F	51	4·5	1·9	2·6	53	B 3	M	59	5·3	3·6	1·7	
	B 15	F	62	6·3	3·9	2·4	+	B 7	M	75	5·3	3·5	1·8	+
	B 16	M	39	6·6	4·7	1·9	++	B 8	M	62	7·0	3·8	3·2	
	B 20	M	54	6·1	3·7	2·4	18	B 11	F	49	4·0	2·9	1·1	
	B 26	M	26	5·1	3·5	1·6	++	B 12	M	64	5·8	3·2	2·6	
	B 27	M	65	5·5	3·8	1·7	30	B 14	M	55	6·6	3·7	2·9	
	B 30	M	48	6·1	4·2	1·9	18	B 19	M	52	6·0	4·1	1·9	
	B 32	M	69	5·7	3·6	2·1	32	B 22	M	62	6·4	4·0	2·4	
	B 34	M	40	6·6	4·5	2·1	++	B 35	M	49	5·9	3·3	2·6	
	B 36	M	50	6·2	3·5	2·7	37							
Siegburg prisoners	S 2	M	23	6·6	4·4	2·2	31	S 1	M	38	7·0	5·0	2·0	
	S 6	M	56	6·3	4·4	1·9	37	S 8	M	29	5·3	3·6	1·7	
	S 11	M	43	6·9	4·3	2·6	+	S 14	M	33	7·1	4·8	2·3	
	S 12	M	38	6·6	5·1	1·5	+	S 19	M	24	6·8	4·4	2·4	
	S 13	M	29	6·0	4·3	1·7	+	S 24	M	21	6·7	4·1	2·6	
	S 15	M	26	6·3	4·7	1·6	31							
	S 17	M	33	6·1	4·8	1·3	27							
	S 18	M	22	5·2	3·6	1·6	23							
	S 20	M	58	5·9	3·7	2·2	30							
	S 22	M	18	7·6	5·2	2·4	26							
	S 25	M	42	6·3	4·2	2·1	29							
Normal controls								C 1	M	25	7·1	4·9	2·2	
								C 8	M	19	7·3	4·6	2·7	
								C 21	M	20	7·1	—	—	
Mean (excluding controls)			41	6·0	4·0	2·0	29			49	6·0	3·8	2·2	

	Groups	Responses	Difference/ Standard error	*P*
Tobacco-mosaic virus	Control and Siegburg	(II, III, IV−I)	3·836	<0·001
		(V, VI, VII−I)	4·203	<0·001
	Control and Barmen	(II, III, IV−I)	4·182	<0·001
		(V, VI, VII−I)	6·722	<0·001
	Siegburg and Barmen	(II, III, IV−I)	0·101	0·92–0·91
		(V, VI, VII−I)	1·292	0·20–0·19

4. In the Siegburg, Barmen and control groups the correlations between age (see Table 3) and rise in titre during the test (i.e. "score" in Table 3) were −0.104, +0.129 and −0.185 respectively. None of these correlation coefficients is significant.

ins and percentage loss of weight

Category 3 (score 2)						Category 4 (score 3 or 4)						
Sex	Age	Serum protein (g./100 c.c.)	Serum albumen (g./100 c.c.)	Serum globulin (g./100 c.c.)	Percentage weight loss	Subject number	Sex	Age	Serum protein (g./100 c.c.)	Serum albumen (g./100 c.c.)	Serum globulin (g./100 c.c.)	Percentage weight loss
M	54	4·9	3·2	1·7	38	B 17	M	43	6·0	3·9	2·1	+
M	49	5·6	3·4	2·2	+	B 31	F	64	6·4	4·1	2·3	42
M	60	5·1	3·3	1·8	40							
M	61	6·9	4·6	2·3	35							
F	48	6·8	4·4	2·4	30							
M	58	6·5	4·6	1·9	+							
M	64	4·2	3·0	1·2	++							
M	25	7·8	5·2	2·6	35	S 4	M	49	6·1	4·1	2·0	++
M	50	5·3	3·2	2·1	33	S 7	M	30	7·0	4·8	2·2	22
M	36	7·2	5·0	2·2	32	S 16	M	52	6·5	4·5	2·0	31
M	56	6·3	4·1	2·2	31	S 21	M	17	7·7	5·4	2·3	23
M	26	5·5	3·9	1·6	25							
M	18	6·6	4·7	1·9	0	C 3	M	34	7·1	4·6	2·5	0
M	22	6·9	4·9	2·0	0	C 4	M	18	6·6	4·4	2·2	0
M	22	7·2	5·1	2·1	0	C 12	M	23	7·3	5·0	2·3	0
F	39	5·8	4·1	1·7	0	C 13	F	20	6·0	4·6	1·4	0
M	22	7·4	4·5	2·9	0	C 15	F	25	6·9	4·8	2·1	0
M	23	7·2	5·0	2·2	0							
M	20	7·4	5·2	2·2	0							
M	25	7·4	5·4	2·0	0							
	50	6·0	4·0	2·0	33			42	6·6	4·5	2·1	29

The essential conclusions from this analysis can be summarized as follows:

In the fowl red cell test, the responses of the Siegburg and Barmen groups did not differ significantly from each other, but they were significantly less than those of the controls in both period (II, III, IV) and period (V, VI, VII).

In the tobacco-mosaic test, the second injection elicited no further mean rise in titre, but the responses of the Siegburg and Barmen groups, which started level with those of the controls, remained well below the latter in periods (II, III, IV) and (V, VI, VII). Again, the responses of the Siegburg and Barmen groups did not differ from each other.

Some attempts have been made to correlate the antibody responses with other data available, but without any positive results. In Table 3 the subjects have been divided into four categories according to the efficiency of their responses measured on a "points" basis, one point being allotted for a rise above an agglutination titre of $\frac{1}{8}$ in period (II, III, IV) or (V, VI, VII) against either antigen. The maximum obtainable was therefore 4, but those scoring 3 or 4 have been put together in the last category to make up a reasonable number. The subjects in the first group scored 0, and those in the intermediate groups scored 1 and 2 respectively.

An examination of the mean values at the bottom of the Table shows that there was no significant correlation between the immunity responses and the concentrations of serum albumen or globulin. Postural and other chance variations in the serum protein level may be partly responsible for this. The percentage loss of weight, which again shows no correlation with antibody production, was derived from the subjects' recollections of their "pre-war" weights. These may not have been very accurate, but are certainly much nearer the truth than they would have been in England, for the figure for his normal weight seems to be graven on the heart of every German over 25. The + and ++ signs indicate that the subjects had so much oedema that their weight was meaningless; but the distribution of + signs throughout the groups shows the same lack of correlation with response as the mean weight losses show. The failure to demonstrate these correlations is not altogether surprising, in view of the known variability of immune responses, and also because a number of subjects whose reactions were essentially normal may have been included in the undernourished groups. The only clear conclusion is that there was an overall reduction in immune responses in the test groups as a whole. The age distribution was not satisfactorily randomized, for the controls were on the whole much younger than the undernourished subjects. There was, however, no correlation between age and response *within* the groups (see Statistical Analysis, section 4), and since immunological literature gives no support to the suggestion that age, except extreme old age, has an influence on the antibody response of adults, it is not considered likely that this factor reduced the significance of the results.

DISCUSSION

The reduction in the efficiency of the antibody-producing mechanism during and presumably as a result of undernutrition is of theoretical interest and is consistent with the animal work described above, but whether it is of practical importance is more debatable. It is unfortunate that a more violent antigenic stimulus was not produced by the experimental antigens. If, as seems reasonable, one assumes that a failure to synthesize globulin is the fundamental cause of the reduced efficiency, one would expect that even a very violent stimulus would be

unable to provoke more than a limited antibody response, owing to lack of protein for building the antibodies. A submaximal stimulus, on the other hand, might in undernutrition provoke only a slower rise in agglutination titre than it does normally owing to the retarded rate of globulin synthesis. Be that as it may, the comparatively small and variable effect of a fairly severe degree of undernutrition on immune responses suggests that a failure to produce antibodies does not play the major part in raising the susceptibility of famished populations to intercurrent disease. It is to be noted, moreover, that while this experiment was being carried out, and in fact during the two years which followed the conclusion of hostilities, there was extremely little epidemic disease in Germany.

SUMMARY

1. The response of a group of 57 undernourished persons to antigenic stimulus is shown to be significantly less than that of a normal control group of 16 subjects.

2. No correlation has been found between immune response and weight loss or the level of serum proteins.

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XII. THE OSMOTIC PRESSURE OF THE SERUM PROTEINS

by R. A. McCance and E. M. Widdowson

It has been recognized, certainly since the first world war, that the proteins are generally below their normal level in the serum of persons with hunger oedema. Many have accepted the connexion as being one of cause and effect, but exceptions have always been admitted, and it has become increasingly clear that normal, or almost normal, serum proteins may accompany extensive nutritional oedema. In an attempt to explain these findings Govaerts and Grégoire (1941) set out to compare the colloidal osmotic pressure of the serum, predicted from the level of albumen and globulin, with the osmotic pressure found by direct measurement. This was really an extension of earlier work in which Govaerts (1927) had shown these values to be in substantial agreement in normal persons and in those suffering from the usual diseases met with in the wards of a general hospital. Govaerts and Grégoire (1941), however, did not find the same agreement in people with nutritional oedema, for in them the predicted osmotic pressures were generally considerably higher than those found by direct experiment. On the basis of these results and of Starling's well-known work on the mechanism of oedema formation, which has been discussed by *McCance* (p. 21), Govaerts and Grégoire explained how oedema could accumulate in the presence of a normal percentage of serum proteins. Their suggestion was essentially a variation of the one which is discussed by *Jones* (p. 211) in connexion with the arginine/lysine ratios, for it implied that undernutrition altered the composition of the serum proteins: "Ces particularités indiquent, soit une changement dans les conditions de précipitation des fractions protéiniques, soit une altération de la structure même de ces protéines. De toute manière, elles montrent que, chez les patients présentant des oedèmes de famine, les protéines sanguines sont profondément altérées dans leur qualité." Although the chemical evidence (*Jones*, p. 211) did not suggest that undernutrition led to extensive alterations in the serum proteins, Govaerts and Grégoire had produced a reasonable explanation of one of the difficult problems connected with nutritional oedema, and it was therefore felt to be desirable to make further measurements of the osmotic pressure of serum proteins and to compare them with the values predicted from the concentrations of albumen and globulin.

METHODS

Serum was taken from three normal and seventeen undernourished persons. Most of these had oedema, and some of them extensive oedema. Blood was usually taken while the subjects were in the recumbent position, but sometimes after they had been standing quietly for some little time. Seven subjects were bled both when they were lying and when they were standing. The osmotic pressure was determined by the method of Hepp (1936) and the serum proteins by the micro-Kjeldahl technique (*Appendix*, p. 401). Govaert's formula was used for calculating the osmotic pressure from the concentrations of the serum proteins. The serum proteins and the osmotic pressure were determined by two different people working independently.

RESULTS

Table 1 contains the results which have been obtained. The figures have been averaged in various ways which will be clear from the Table. The predicted

TABLE 1

Relationship between the osmotic pressure of the serum calculated from the levels of albumen and globulin, and the osmotic pressure determined by experiment

Subject No. and posture	Grade of oedema	Serum proteins (g./100 c.c.)			Osmotic pressure (mm. H_2O)	
		Total	Albumen	Globulin	Calculated	Observed
Normal controls						
C 24 lying ..	0	7·16	5·05	2·11	422	430
C 25 „ ..	0	6·85	4·35	2·50	377	387
C 26 „ ..	0	7·38	4·85	2·53	409	391
Undernourished subjects						
B 135 lying	3	5·61	3·78	1·83	322	314
B 135 standing	3	6·59	4·42	2·17	375	387
B 142 lying	3	6·45	3·91	2·54	346	345
B 142 standing	3	6·70	4·22	2·48	367	361
B 176 lying	3	6·23	4·49	1·74	372	381
B 176 standing	3	6·92	5·06	1·86	417	400
B 177 lying	0	6·75	4·25	2·50	370	368
B 177 standing	0	7·05	4·50	2·55	390	423
B 178 lying	2	5·72	3·79	1·93	324	302
B 178 standing	2	6·22	4·22	2·00	357	342
B 180 lying	1	5·66	3·90	1·76	328	318
B 180 standing	1	7·15	4·74	2·41	405	390
B 182 lying	3	5·45	3·23	2·22	287	292
B 182 standing	3	6·08	3·53	2·55	317	329
X 19 lying	4	6·32	4·05	2·27	349	320
B 138 „	1	5·48	3·68	1·80	313	303
B 139 „	2	6·00	3·22	2·78	286	322
B 140 „	2	4·52	2·45	2·07	225	256
B 168 „	3	6·20	4·38	1·82	365	378
B 169 „	3	6·20	4·11	2·09	352	346
B 170 „	2	6·42	4·38	2·04	370	357
B 155 standing	4	5·06	3·01	2·05	268	260
B 179 „	1	8·00	5·13	2·87	443	466
B 181 „	3	6·20	3·86	2·34	344	336
Average: Normal controls		7·13	4·75	2·38	403	403
„ B 135–182 lying		5·98	3·91	2·07	336	332
„ B 135–182 standing		6·67	4·38	2·29	377	378
„ All undernourished subjects		6·21	4·00	2·19	345	346

values were not higher than the observed, in fact the agreement between the two was good. This statement applies to the undernourished as well as to the normals. It also applies to the individuals who were studied both lying and standing, and the effect upon the serum proteins that usually follows a change of posture can be seen at a glance from the averages. It can also be seen that the change in serum proteins was accompanied by a corresponding change in the observed osmotic pressure. There is, therefore, nothing in these results to support the contention of Govaerts and Grégoire, and some other explanation must be found for the presence of oedema and normal serum proteins in the same person. These results, moreover, exclude any gross change in the composition of the serum proteins on assuming the erect posture. A change of this nature might have been held to account for the way in which oedema accumulates during the day and disappears during the night or with rest in bed.

It would appear from the paper of Govaerts and Grégoire (1941) that their claims were based upon a study of 27 patients, all suffering from nutritional oedema. No normal subject seems to have been investigated in 1941, and the normal data appear to have been taken from the earlier work of Govaerts in 1927. Had the membranes been faulty in 1941, Govaerts and Grégoire might easily have obtained a series of results for the observed osmotic pressures which were lower than those obtained in 1927.

In view of these differences a visit was paid by the authors to Professors Govaerts and Grégoire to see if the discrepancies could be resolved. Their original notebooks were placed at our disposal, and although no real explanation was discovered one point of considerable interest did arise, namely that their albumen/globulin ratios were considerably lower than ours.

SUMMARY

The measured osmotic pressure of the serum proteins during undernutrition has not been found to differ from the pressure calculated from the concentrations of albumen and globulin by the formula of Govaerts.

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XIII. THE ELECTROPHORETIC ANALYSIS OF SERA

by R. A. Kekwick

No adequate series of electrophoretic measurements on sera from undernourished persons has previously been reported. The following is an account of the examination of the sera from 16 undernourished men. Four (K3, 10, 14, 15) were prisoners in a civilian gaol at Kiel, three (L3, 5, 6) were patients in the Langenhorn hospital in Hamburg, and seven (N2, 4, 6, and W2, 4, 5, 10) were inmates of two civil internment camps. The blood samples from these 14 subjects were collected in April 1946 (*McCance and Widdowson*, p. 1). The remaining two (R2 and 3) were repatriated prisoners of war from Russia and were examined in Wuppertal in February 1948.

These men, except for the two repatriated prisoners of war, were among the most undernourished people seen by members of the Unit in Germany. All but one of them stated that they had lost more than 20 per cent of their previous weights, and their appearance fully supported their statements.

METHODS

Treatment of Sera

Freshly drawn sera were stored at −25° C. until required for examination. They were then rapidly thawed in a bath at 25° C. and a measured volume dialysed to equilibrium at 2° C. against phosphate buffer *p*H 8·0, ionic strength I = 0·2. The dialysed sera were made up quantitatively to 15 c.c. with buffer in a volumetric flask, and the refractive increment of the dissolved protein, n, determined with a dipping refractometer at 25·0° C. using the Hg green line (λ = 546 mμ). The refractive increment was obtained from the expression $n = n_1 - n_0$ where n_1 is the refractive index of the dialysed serum, and n_0 the refractive index of the buffer. The refractive increment due to protein in the untreated serum was calculated from n and the dilution factor.

Electrophoretic Measurements

For electrophoretic examination dialysed sera were diluted with buffer to give a solution whose refractive increment was 0·00400. Electrophoretic measurements were made in the Tiselius (1937) apparatus at 0·5° C. with a potential gradient of about 5 V. per cm. Optical observations were made with the diagonal Schlieren method (Philpot, 1938), the light source being a mercury arc from which monochromatic light λ = 546 mμ was isolated. Photographs of the Schlieren diagrams were taken on Ilford half-tone panchromatic plates.

Tracings from the photographs were made with a magnification of eight diameters and analysed geometrically. The analytical figures given are the percentages of the total protein attributable to the various components, and are the mean of the values from the ascending and descending limb diagrams.

Ultracentrifuge Measurements

Some of the sera were examined in the Svedberg oil turbine centrifuge, using a 12 mm. cell at a field strength of 270,000 times gravity. The optical and photographic recording was similar to that described for the electrophoresis measurements.

For these experiments the dialysed serum was diluted to give a protein refractive increment of 0·00300, the solvent being phosphate buffer *p*H 8, I = 0·2, with in addition 0·15 M sodium chloride.

TABLE 1

Electrophoretic analysis of sera

Column:	1	2	3	4	5	6	7	8	9
Serum	Total Protein $n = n_1 - n_0$	Albumen (% total protein)	Globulins (% total protein) α	β	γ	Oedema	Albumen (n_a)	Total protein (g./100 c.c.)	Albumen
K 3	0·01338	58·6	10·5	16·7	14·3	++	0·00784	7·04	4·13
K 10	0·00914	52·9	12·6	15·7	18·8	+	0·00484	4·81	2·55
K 14	0·00876	54·8	10·1	19·7	15·5	+++	0·00480	4·61	2·53
K 15	0·00898	58·2	11·9	13·3	16·7	+	0·00523	4·73	2·76
L 3	0·01073	58·0	5·8	21·9	14·4	0 Past +	0·00622	5·65	3·27
L 5	0·00874	37·0	13·1	19·5	30·5	+ Past +++	0·00323	4·60	1·72
L 6	0·00896	52·6	9·8	23·0	14·8	+ Past +++	0·00471	4·72	2·48
N 2	0·00876	63·9	4·9	16·4	14·7	++	0·00560	4·61	2·95
N 4	0·01120	62·1	10·7	10·0	17·3	+	0·00696	5·89	3·66
N 6	0·01092	61·3	14·5	11·7	12·6	++	0·00669	5·75	3·53
W 2	0·01148	58·3	9·0	21·3	11·5	0	0·00669	6·04	3·53
W 4	0·01573	65·5	6·6	12·5	15·6	0	0·00669	8·28	5·42
W 5	0·01508	58·9	8·6	16·5	16·2	0	0·00887	7·93	4·67
W 10	0·01153	56·0	5·7	19·1	16·1	++	0·00646	6·07	3·40
R 2	0·01442	60·5	8·2	13·9	17·5	0	0·00872	7·59	4·59
R 3	0·01462	59·2	8·1	9·6	23·2	0	0·00866	7·69	4·56
Normal	0·01350	65·1	6·4	15·1	13·6		0·00879	7·11	4·63
Mean values		58·7	9·1	16·1	15·9				
S.D.		3·9	2·7	4·1	2·9				
Coefficient of variation		6·5	29·7	25·4	18·3				

RESULTS AND DISCUSSION

The data relating to 16 cases of undernutrition are presented in Table 1, with the values for normal pooled human serum for comparison.

In calculating the mean values and standard deviation for the components (columns 2, 3, 4, and 5) serum L5 was neglected because it showed a pattern grossly divergent from those of the remaining 15 sera.

Column 7 gives the refractive increment due to albumen (n_a), obtained from the data of columns 1 and 2. The data of columns 8 and 9 were derived from columns 1 and 7 by assuming the specific refractive increment of all the proteins to be 0·00190. This value is approximately that for human serum albumen (Perlmann and Longsworth, 1948).

Examination of the percentage of total protein attributable to albumen and α-, β-, and γ-globulins over the whole series reveals no consistent deviation from the normal for any one of these components, other than a tendency to a slight reduction in the proportion of albumen. Though the total percentage of the globulins shows a slight corresponding increase, this is not associated with any particular component.

The electrophoretic analyses of the sera from three cases of hunger oedema are given in a paper by Gsell (1945). Each of these shows a marked decrease in the albumen, with values between 49 and 54 per cent of the total protein, and a considerable increase in the γ-globulin, with values from 24 to 32 per cent. In fact, the sera resemble the serum of case L5, which diverges grossly from the remainder of the present series. It seems possible that this type of divergence, with a very high proportion of γ-globulin, may be not a direct consequence of undernutrition but the result of an intercurrent infection or possibly liver damage.

Albumen is the predominant factor controlling the level of the colloidal osmotic pressure of serum because of its high proportion in the serum and because its molecular weight is the lowest of the serum proteins. The figures in Table 1, col. 9 were calculated to see if any direct correlation existed between the concentration of albumen and the occurrence of oedema. That this was not the case is evident; for example, in S6 and W2 the albumen concentrations were identical, yet one was associated with oedema, the other not. Again, K3 was oedematous although his albumen concentration was almost normal.

The ultracentrifugal examination of several of the sera gave no suggestion that the molecular weight of the serum proteins was lower than normal. Such a change, if it occurred, would tend to maintain the colloidal osmotic pressure in spite of a fall in the total serum protein.

These conclusions are in agreement with those of *McCance and Widdowson* (p. 204), who measured the osmotic pressure directly.

SUMMARY

1. Electrophoretic findings are presented for 16 sera from cases of undernutrition.

2. The distribution of the electrophoretic components showed no consistent deviation from normal except a slight reduction in the proportion of albumen.

3. There was no direct correlation between the concentration of albumen in the sera and the occurrence of oedema in the patients.

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XIV. THE RATIO OF ARGININE TO LYSINE IN THE SERUM PROTEINS

by P. E. H. Jones

Two Belgian investigators, Florkin and Duchateau (1944), claimed that the molecular ratio of arginine to lysine in the serum proteins might be lowered by undernutrition. In two normal individuals ratios of 10/19 were found, while in six patients suffering from nutritional oedema the ratio varied between 10/19·4 and 10/44. Experiments were also carried out on dogs. Animals which had been fed for 27 to 45 days on turnips (100 g. per kg. of body weight per day) developed oedema with ascites and hydrothorax. In the serum of one of these dogs the molecular ratio of arginine to lysine was 10/49, and in the sera of three others it was in the region of 10/30. In two normal dogs ratios of 10/22·5 were found.

To place these findings in their true perspective it is necessary to go back to 1912. In that year McCollum suggested that when an animal was subjected to a protein deficiency a partial hydrolysis of some of the tissue proteins might take place to make amino-acids available for the proteins of other more vital organs. This implied that starvation might alter the arrangement and number of amino-acids in the molecules of some of the body proteins. Two years later Osborne and Mendel (1914) put forward essentially the opposite point of view, namely that "the tissues either form a typical protoplasmic product or none at all". Since that time the matter has been investigated by several different people, but contradictory results are still being obtained. After working on the effects of starvation and protein deficiency on the composition of the tissue proteins, Roche (1933a,b; 1934a,b) came to the conclusion that the amount of lysine in the muscle of rats which had died of protein deficiency was about 40 per cent below the normal figure (Kosterlitz and Campbell, 1945), and that the percentages of tryptophan and tyrosine were also below their normal values. The amount of cystine was not significantly changed (Roche, 1934a). Schenck and Wollschitt (1933a,b) found that total starvation reduced the tryptophan and raised the cystine in rat muscle. However Lee and Lewis (1934) and Louis and Lewis (1944), the latter working on rabbits, were unable to confirm any of these observations. Block, Darrow and Cary (1934) found that the molecular ratio of arginine to lysine in the serum proteins of mammals (man, dog, cow) was extraordinarily constant (10/18) in spite of wide variations in the total serum proteins and in the albumen/globulin ratio. Subsequently Block (1940) failed to confirm the claims of Dirr and Strehle (1939) that arginine, administered either orally or intravenously, increased the percentage of this amino-acid in the proteins of human serum (see also Schenck and Wollschitt, 1933b). Bálint and Bálint (1940b; 1941) fractionated and analysed human serum proteins on an extensive scale. In one case of hypoproteinaemia they found roughly twice the normal amounts of tyrosine and tryptophan in the albumen fraction (1940a). They did not study any cases of undernutrition with oedema, but Kühnau (1946), basing his work on that of the Bálints, claimed that in nutritional oedema the serum proteins were deficient in cystine, methionine and tyrosine. The tone of Kühnau's article may be gauged by his statement that "Die Existenz unseres Volkes . . . wird erneut durch den Eiweissmangel gefährdet", and his results should probably be accepted with reserve.

The present investigation was undertaken specifically to confirm or refute the findings of Florkin and Duchateau.

MATERIAL AND METHODS

Serum was obtained from six well-nourished persons, two of them laboratory workers and four of them English hospital patients, and from eleven undernourished German adults who were suffering from oedema of nutritional origin. Serum protein estimations were made by the copper sulphate specific gravity method of Phillips, van Slyke, Dole, Emerson, Hamilton and Archibald (1945), and also by the micro-Kjeldahl technique (see p. 401). Arginine and lysine were determined by the method of Gale (1945; 1946). Protein hydrolysates were prepared by diluting 5 c.c. of serum with an equal volume of distilled water; 10 c.c. of 10 N-HCl were added and the mixture boiled for 20 hours under a reflux condenser. The hydrolysate was evaporated to dryness *in vacuo*. It was then taken up in water and re-evaporated to dryness *in vacuo* five successive times to remove HCl. The *p*H of the residue was adjusted to about 5·6 with CO_2-free 2 N-NaOH and the final volume was made up to 5 c.c. with water.

Estimation of l (+) Arginine

0·5 c.c. of the serum hydrolysate and 2·0 c.c. of 0·2 M-citrate-phosphate buffer *p*H 5·2 were put into the main cup of a standard Warburg manometric flask. The side-bulb carried about 40 mg. of l (+) arginine decarboxylase preparation suspended in 0·5 c.c. of the same buffer. After a period for equilibration the solutions were mixed. Evolution of carbon dioxide ceased in about 20 minutes. The volume of carbon dioxide which was liberated represented 95 per cent of the theoretical yield (Gale, 1946). The quantity of arginine was calculated on this basis.

Estimation of l (+) Lysine

This was measured at a *p*H of 6·0 at which there is an appreciable retention of dissolved carbon dioxide, so the "acid tip" method (Woods and Clifton, 1937) was employed. Into the main cups of two double side-bulb manometric flasks were measured 0·25 c.c. of the serum hydrolysate and 2·0 c.c. of 0·2 M-phosphate buffer, *p*H 6·0. One side-bulb carried about 20 mg. of l (+) lysine decarboxylase preparation suspended in the same buffer, the other 0·25 c.c. of 4 N-H_2SO_4. In the experimental manometer the enzyme was "tipped" immediately after equilibration, and about 20 minutes later, or when no more carbon dioxide was being evolved, the acid was "tipped" to liberate any dissolved gas. In a control manometer, set up in exactly the same way, the acid was "tipped" first, and the enzyme immediately afterwards. Any carbon dioxide evolved as a result of interaction of the reagents was subtracted from the total evolution in the experimental manometer.

RESULTS

Table 1 gives the results obtained for the English controls and for the group of individuals suffering from undernutrition with oedema. There were apparently small changes in the absolute amounts both of lysine and arginine in the serum proteins, but it will be observed that the ratios were all of the same order as those obtained by Block *et al.* (1934) and those regarded by Florkin and Duchateau (1944) as normal. There was, moreover, no significant difference between the two groups. The nutritional state of the individual, therefore, appeared to have no effect on the molecular ratio of arginine to lysine, so that the results were not the same as those of Florkin and Duchateau (1944).

TABLE 1

Arginine/lysine ratios in serum proteins

Subject No.	Posture*	Grade of oedema or physical state	Serum protein (g./100 c.c.)	Arginine (millimol/g. serum protein)	Lysine (millimol/g. serum protein)	Molecular ratio Arginine/ Lysine
		Undernourished subjects				
X 19	Standing	4	6·32	0·330	0·698	10/21·2
B 88	Lying	3	5·10	0·321	0·617	10/19·2
B 138	Lying	1	5·48	0·355	0·746	10/21·0
B 139	Lying	2	6·00	0·330	0·785	10/23·7
B 140	Lying	2	4·52	0·354	0·783	10/22·1
B 141	Lying	1	6·10	0·374	0·844	10/22·6
B 152	Lying	2	6·90	0·355	0·701	10/19·8
B 160	Lying	3	6·02	0·352	0·760	10/21·6
B 163	Lying	0	6·57	0·359	0·824	10/23·0
B 135	Lying	3	5·61	0·363	0·824	10/22·7
	Standing	3	6·59	0·338	0·725	10/21·5
B 155	Lying	2	4·57	0·357	0·673	10/18·9
	Standing	4	5·06	0·356	0·713	10/20·2
		Control subjects				
C 25	Lying	Healthy	6·85	0·335	0·707	10/21·1
C 28	Lying	Traumaticeffusion of knee	6·37	0·340	0·705	10/20·8
C 29	Lying	Osteoarthritis	6·30	0·353	0·712	10/20·2
C 30	Lying	Fracture of metatarsal	6·49	0·377	0·797	10/21·2
C 31	Lying	Osteoarthritis of spine	6·12	0·349	0·828	10/23·8
C 27	Lying	Healthy	6·40	0·376	0·765	10/20·4
	Standing	Healthy	7·10	0·355	0·692	10/19·5

* See Widdowson and McCance (1950 and p. 165).

In 1949 the opportunity arose of discussing these results personally with Professor Florkin, and through his courtesy two samples of dried dog serum which had been analysed many years before were provided for an investigation of their arginine/lysine ratios by the methods described in this paper. One of these had been taken from the normal dog for which a ratio of 10/22·5 had been found (Florkin and Duchateau, 1944); the other sample came from one of their undernourished dogs and had previously yielded an abnormal value of 10/31. These two sera were treated as described above except that, since they were in the dry state, an additional 5 c.c. of water was added before the hydrolysis. The ratio obtained for the normal dog's serum was 10/19·4, a value which fell within the normal range and agreed fairly well with Florkin and Duchateau's result. The serum of the undernourished dog, however, gave an arginine/lysine ratio of 10/14·8. Far from being high this result was low by any standard, and it is suggested that the high ratios found by Florkin and Duchateau may have been due to some unsuspected technical difficulty in the chemical methods employed.

DISCUSSION

In Table 1 it will be seen that the molecular ratios of arginine to lysine lay between 10/18·9 and 10/23·8. In a biological series some variation is to be expected, and the results obtained are in accordance with such an expectation for normal variation within a single species. The mean value of the ratio is slightly higher than that recorded either by Block *et al.* (1934) or by Florkin and Duchateau (1944) for normal serum. This may be due to difference of method. Racemization of one or both amino-acids during hydrolysis must be noted as a possible source of slight but consistent error in the results now being reported, but there is no certain evidence on this point.

These results, therefore, do not indicate that changes in the composition of the tissue proteins are an essential part of the oedema of undernutrition (Herken and Remmer, 1947; *McCance*, p. 21). It is doubtful, indeed, if such changes occur, and it is probable that Himsworth (1946) was correct in stating that "alterations in the quantity or quality of dietary protein may influence the amount of the different tissue proteins formed, but they will not apparently induce the body to form imperfect or unusual protein molecules".

SUMMARY

The arginine/lysine ratios of the serum proteins have been found to be within normal limits in undernutrition.

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XV. SERUM CHOLINESTERASES

by Audrey O. Hutchinson, R. A. McCance, and E. M. Widdowson

The basis of the cholinesterase molecule, like that of all other known enzymes, is a protein, and since undernutrition has long been known to lower the level of serum proteins it was decided to find out if it had any effect on serum cholinesterase. No systematic work had been done on this subject, but Milhorat (1938) noted that the cholinesterase activity of the serum of one woman with anorexia nervosa varied with her well-being and body weight, and Kaswin (1945), who had investigated a variety of pathological material, had found lowered activities in people with famine oedema. Faber's (1943) study of a single individual had also suggested that undernutrition and loss of weight might substantially reduce the concentration of enzyme in the serum. When they were first in Germany, Widdowson and McCance also studied alkaline phosphatase, but since they found the sera of normal and undernourished men to have similar activities they abandoned the study of this enzyme and concentrated on cholinesterases. Both the "true" or T-enzyme (Mendel, Mundell and Rudney, 1943) and the unspecific "pseudo" or P-enzyme have been studied.

SUBJECTS

The subjects for these tests and experiments were (*a*) healthy British men who were working in Germany or Cambridge and who were eating army or civilian rations; (*b*) 24 German civil internees, 12 of whom had oedema when the blood was taken in the spring of 1946; (*c*) 15 civil prisoners in a gaol at Kiel, who were very undernourished when they were seen in April 1946; (*d*) 17 civil prisoners at Siegburg; (*e*) 82 employees of the I.G. Farben works at Elberfeld in the summer of 1946; these men were undernourished, but were less so than many of the other inhabitants of Wuppertal, for they were in employment, and the firm provided a canteen dinner and assisted its workers in other ways; (*f*) a series of civilians who attended the unit's clinic at the Städtisches Krankenhaus, Barmen, at various times from 1946 to 1948; (*g*) German prisoners of war repatriated from Russia.

Observations were made on the effects of changes in diet, some of which were produced experimentally, on the serum cholinesterase levels of men in groups (*d*) (*f*), and (*g*).

In addition to the work on man, experiments were also carried out on rats and dogs. The former were inbred black and white animals originally obtained from the strain kept at the Lister Institute, and the latter were mongrels obtained from the animal department of the I.G. Farben laboratories.

METHODS

The serum was separated from the corpuscles soon after the clot had formed and stored at 4° C. until the measurements were made. Kept in this way the cholinesterases appeared to retain all their activity for at least a year, even if the serum had not been collected aseptically. No estimation of the activity of the T-enzyme was made on a sample of serum if it showed any signs of haemolysis. The activity of the T-enzyme was determined manometrically using acetyl-β-methyl-choline chloride as the substrate. Ringer bicarbonate replaced the sodium bicarbonate used by Mendel *et al.* (1943). The activity of the P-enzyme was determined by McArdle's (1940) technique and the present

results should be strictly comparable with his. The activities were expressed as the number of c.mm. of carbon dioxide liberated per c.c. of serum per minute.

Technical Investigations

1. *Spontaneous variations from day to day.* Specimens of blood were taken from three normal men, daily for the first three days, every other day for the next six, a week later and then a fortnight after that. The variations never exceeded five units, and all the standard deviations were less than two units. Determinations were made of the activity of the serum of several men at intervals of three, six, and twelve months. The activity rarely deviated by more than 5 per cent, which was not much more than the experimental error of the method.

2. *The effect of posture on the activity of the enzymes.* Specimens of blood were taken from seven normal and eight undernourished persons while they were still in bed in the morning and after they had stood quietly for two hours. Total protein concentration and the activity of the P-enzyme were determined on each sample of serum. The results are shown in Table 1. Standing raised the

TABLE 1

The effect of posture on the concentration of serum proteins and on P-cholinesterase activity

Normal subjects	Lying in bed		After standing for 2 hours	
	Total protein (g./100 c.c.)	P-cholinesterase (c. mm. CO_2/ c.c./min.)	Total protein (g./100 c.c.)	P-cholinesterase (c.mm. CO_2/ c.c./min.)
1	7·45	67	7·85	63
2	6·30	85	7·05	98
3	6·70	61	7·85	61
4	6·90	81	7·85	86
5	6·70	62	7·45	66
6	6·70	58	7·45	61
7	7·05	106	7·85	98
Average	6·83	74	7·62	76
Undernourished subjects				
1	6·30	69	7·45	70
2	7·05	58	7·45	58
3	6·30	55	7·45	61
4	7·05	67	8·25	71
5	5·90	43	6·30	43
6	5·50	57	6·70	58
7	7·05	69	7·45	70
8	6·90	43	7·05	54
Average	6·51	57	7·26	61

concentration of the serum proteins by about 12 per cent in both groups and each individual showed an increase, but the activity of the P-enzyme was only raised by an insignificant amount in both the normal and the undernourished men. There were men in both groups who showed a slight fall in cholinesterase

activity after they had stood for two hours. Hence changes of posture altered the activity of the enzyme much less consistently than they altered the concentration of serum protein. It is not clear why this should have been so, but it meant that when dealing with averaged results postural effects could generally be disregarded.

TABLE 2

Variation of P-cholinesterase level in the serum with state of nutrition

Subjects	Clinical assessment	Serum proteins (g. per 100 c.c.)			Activity of P-enzyme units	
		Total	Albumen	Globulin	Average and range	Standard deviation
37 British men ..	Normal	7·27	5·06	2·21	79 (59–122)	15·1
82 I.G. Farben employees ..	Slightly undernourished	6·82	—	—	57 (20–117)	14·5
45 Civilian applicants for rations on account of oedema ..	More undernourished than previous group	6·00	3·79	2·21	49 (26–99)	16·2
17 Prisoners at Siegburg ..	Undernourished	6·51	4·49	2·02	49 (28–88)	16·0
12 Civil internees	Undernourished without oedema	7·18	—	—	61 (39–105)	20·3
12 Civil internees	Undernourished with oedema	6·04	—	—	42 (25–56)	8·1
6 Prisoners at Kiel	Very undernourished without oedema	7·23	—	—	46 (29–58)	10·1
6 Prisoners at Kiel	Very undernourished with oedema	4·75	—	—	29 (15–40)	7·7

RESULTS

P-Cholinesterase and Nutritional Status in Man

Table 2 shows some of the results that were obtained by the investigation of groups of men at what were known to be different levels of nutrition. The average for the normal series (79 units) was very close to that of McArdle (78 units). The average for the I.G. Farben workers in 1946 was substantially lower (57 units) and that of the civilian applicants for extra rations was lower still (49 units): the former group was clinically the better nourished. At the bottom of the Table are the results that were obtained at some civil internment camps and at Kiel gaol in the spring of 1946. In both the state of nutrition of the inmates was very poor, although they did not all have oedema, and the figures for those with and without oedema have been given separately. There was a strong tendency for the mean activity of each group to reflect the clinical assessment of the nutritional status of that group. It was not possible to give any quantitative expression to this, but the groups in Table 2 are arranged in what was thought clinically to be the order of descending nutritional status.

and it will be seen that the mean cholinesterase activities are in almost exactly the same order.

The mean results for serum proteins of each group are also given in Table 2. They showed the same tendency to fall with the state of nutrition as estimated clinically, except that the two very undernourished sub-groups without oedema each had serum proteins within the normal range.

The Effect of Changes in Diet on the Serum Cholinesterases in Man

The essential findings from a number of observations and experiments have been collected together in Table 3, but a few words of explanation and expansion seem to be necessary. The observations at Siegburg were not a planned experiment, but the improvement in the official rations for prisoners provided the necessary change of conditions. The increase in Calories was mainly due to an increased ration of bread and potatoes. The rise in the prisoners' body weights and in the esterases was considerable, but the men could not have been described as well-nourished when the second test was made and the average activity of the P-enzyme was still below normal. The experiment on the 19 civilians has been described by *Widdowson* (p. 313). The Table brings out clearly the effect of (*a*) the first-class diet which provided 6,000 Calories per day for two months, (*b*) the return to home surroundings and a very restricted diet, (*c*) the gradual return of "plenty". In each case the body weights and the cholinesterases varied together. There were some interesting individual records among these men. On their return to home surroundings, for example, three of the men managed to maintain their weight better than the others and their cholinesterases fell less than the average of the others.

The next three experiments were undertaken to see if the forced metabolism of any of the major dietary constituents brought about rapid or conspicuous changes in the cholinesterases. The possible association of the non-specific pseudo enzyme with the metabolism of fat led to the first trials being made with fat. The basal diets contained very little fat, only some 20 g. per day, so that the supplements were considerable. In spite of this, the results were in a sense negative, in that the increase in the cholinesterase activity was small and much more in keeping with the small increase in body weight than with the very large amounts of fat being digested and metabolized. The third of these experiments was carried out to study the effect of a large increase in the intake of animal protein. The protein was added to the diet in the form of bully beef, cheese, and milk, and some fat and carbohydrate were therefore included in the supplement. The additional Calories amounted to about 1,700 per day, and this was also the approximate Calorie value of the 200 g. of margarine used in the previous experiment. The results again showed that the rise in the cholinesterases appeared to be coupled with that of the subjects' body weights. It was not specifically related to the metabolism of additional protein.

The last investigation was made on repatriated prisoners of war and the men were sent to Wuppertal for this experiment as soon as they reached the frontier station. They were undernourished, but not nearly as badly as many who had come back in 1947, and during the period of observation they ate enormous quantities of food (*Widdowson and Thrussell*, p. 296) and became fat. The Table brings out clearly the changes in their body weights and cholinesterases. It is to be noted that by the end their average P-cholinesterase activity was well over the 76 units which was the average for the 28 controls. The average T-cholinesterase activity for the repatriated prisoners was also above the normal

TABLE 3

The effect of changes of diet on the serum cholinesterases

Subjects	Diet before change	Initial data			Alteration of diet	Duration of change	Final data			Significance of change	
		Weight (kg.)	P-cholin-esterase units	T-cholin-esterase units			Weight (kg.)	P-cholin-esterase units	T-cholin-esterase units	P-cholin-esterase	T-cholin-esterase
12 male civilian prisoners, Siegburg gaol	Official rations	55·3	52 S.D. 18·6	0·807 S.D. 0·143	Improvement in rations mostly more bread and potatoes	5 months	65·8	63 S.D. 18·0	1·05 S.D. 0·127	$t = 2{,}56$ $P = 0{\cdot}05 - 0{\cdot}02$	$t = 4{\cdot}43$ $P = <0{\cdot}01$
19 male civilians (see *Widdowson*, p. 313)	Official rations and some supplements	58·3	47 S.D. 7·7	0·917 S.D. 0·127	Unlimited food	2 months	69·0	75 S.D. 13·0	1·02 S.D. 0·145	$t = 12{\cdot}2$ $P = <0{\cdot}01$	$t = 2{\cdot}63$ $P = 0{\cdot}02 - 0{\cdot}01$
	Unlimited food	69·0	75 S.D. 13·0	1·02 S.D. 0·145	Return to home conditions	5 months	62·5	55 S.D. 11·5	0·969 S.D. 0·145	$t = 6{\cdot}6$ $P = <0{\cdot}01$	not sig.
	Official rations and some supplements	62·5	55 S.D. 11·5	0·969 S.D. 0·145	Slow improvement in rations and economic conditions	7 months	67·0	67 S.D. 8·3	1·032 S.D. 0·116	$t = 2{\cdot}70$ $P = 0{\cdot}02 - 0{\cdot}01$	not sig.
6 male civilians	Hospital rations (approx. 1,700 Cals.)	—	56 S.D. 23·1	0·936 S.D. 0·291	Hospital rations and 100 g. margarine/day	3 days	—	59 S.D. 17·7	1·012 S.D. 0·220	$t = 3{\cdot}27$ $P = 0{\cdot}05 - 0{\cdot}02$	not sig.
6 male civilians	Home rations followed by hospital rations (1,700 Cals.)	64·4	47 S.D. 11·5	0·761 S.D. 0·170	Hospital rations and 200 g. margarine/day	6 weeks	67·5	54 S.D. 13·7	0·804 S.D. 0·182	$t = 4{\cdot}08$ $P = < 0{\cdot}01$	not sig.
6 male civilians	Home rations followed by hospital rations (1,700 Cals.)	59·4	45 S.D. 4·8	0·780 S.D. 0·116	Hospital rations and 200 g. skimmed milk powder, 250 g. corned beef and 150 g. cheese/day	6 weeks	62·1	54 S.D. 8·0	0·793 S.D. 0·124	$t = 3{\cdot}31$ $P = 0{\cdot}05 - 0{\cdot}02$	not sig.
6 repatriated prisoners of war	Unknown. On transport	56·3	45 S.D. 6·0	0·955 S.D. 0·045	Hospital rations, supplementary rations, and extra food brought by visitors	16 days	59·1	63 S.D. 7·1	—	$t = 6{\cdot}59$ $P = <0{\cdot}01$	—
		56·3	45	0·955		30 days	65·2	76• S.D. 5·1	—		—
		56·3	45	0·955		46 days	69·2	84† S.D. 3·2	—	—	—
		56·3	45	0·955		53 days	71·4	89‡ S.D. 5·1	1·222 S.D. 0·107		$t = 5{\cdot}24$ $P = <0{\cdot}01$

• 63 to 76 $t = 5{\cdot}17$ $P = <0{\cdot}01$
† 76 to 84 $t = 7{\cdot}74$ $P = <0{\cdot}01$
‡ 84 to 89 $t = 4{\cdot}10$ $P = <0{\cdot}01$

average, which was 1·024 units. After obtaining these results, 17 other repatriated prisoners who had become fat and who had swollen parotid glands (*McCance, Dean and Barrett*, p. 135) were weighed and measured and a sample of blood was taken for the determination of the activities of both the serum cholinesterases. The average height of these men was 1·73 m. and the average weight 75·3 kg. The activity of the P-enzyme averaged 96 units (S.D. 9·26), which was significantly higher than the normal average ($t = 5·50$, $P = <0·01$). The average activity of the T-enzyme was 1·323 units (S.D. 0·321), which was also significantly higher than the normal average ($t = 3·87$, $P = <0·01$).

Table 3 brings out another point. The changes in the P-enzyme were usually considerably greater than those of the T-enzyme, and although the changes were always in the same direction those of the T-enzyme were often not significant.

Comparative Changes in Cholinesterase Activity and Serum Proteins

If the cholinesterase molecule is a protein, variations in its activity must to some extent be ordered by changes in the concentration of that fraction of the serum proteins with which it is physically associated. It might even be supposed that the fall in activity brought about by undernutrition was merely a reflection of the fall in the serum proteins, which has so often been demonstrated. This relationship has been examined from time to time and the data bearing upon it may be set out as follows:

(1) A change of posture may make a considerable difference to the concentration of proteins in the serum without altering the activity of the cholinesterase to a comparable extent (Table 1).

(2) Undernutrition lowers the activity of P-cholinesterase much more than the concentration of serum proteins, and conversely a return to a plentiful diet may raise the cholinesterase to very high levels without making much difference to the concentration of serum proteins. Thus: (*a*) Table 2 shows that mean falls in cholinesterase activity from 79 to 42 and to 29 units were accompanied by falls of serum proteins only from 7·27 to 6·04 and 4·75 per 100 c.c. (*b*) The serum of two of the most undernourished sub-groups in Table 2 had perfectly normal serum proteins, but had cholinesterase activities of 61 and 46 units, both considerably below the normal. (*c*) The experimental work carried out on the repatriated prisoners showed that great increases in cholinesterase activity were accompanied by quite minor changes in the concentration of serum proteins. A mean rise in cholinesterase activity, for example, from 45 to 89 units was associated with a mean rise in the concentration of serum proteins from 6·73 to 7·43 g. per 100 c.c.

TABLE 4

A comparison of the enzyme activities in the serum of pairs of people with similar concentrations of serum proteins

Pair	Total protein (g./100 c.c.)	Albumen (g./100 c.c.)	P-cholinesterase units	T-cholinesterase units	Total protein (g./100 c.c.)	Albumen (g./100 c.c.)	P-cholinesterase units	T-cholinesterase units
1	4·56	3·11	27	0·50	4·69	2·72	44	1·10
2	6·25	4·24	30	0·59	5·85	3·80	59	0·89
3	5·59	2·87	30	0·83	5·70	3·65	66	0·89
4	5·12	3·07	31	0·52	5·08	3·45	57	1·20
5	5·55	3·64	42	0·29	5·50	3·30	58	0·84

(3) People with similar concentrations of albumen or of total protein in their sera sometimes had widely different enzyme activities. Table 4 has been constructed by selecting five pairs of subjects from a group of 22 undernourished men so that there were roughly the same concentrations of albumen and of total protein in the sera of each pair. A glance at the Table shows that the individuals forming each pair had very different esterase activities.

This evidence makes it clear that the changes in cholinesterase activity, and particularly the fall in human undernutrition, are something quite apart from the well-known but much smaller changes in the serum albumen and globulin.

Experiments with Rats

Two groups of five adult male rats, made up from pairs of littermates of approximately equal weights, were used for these experiments. One group was given the usual amounts of the stock diet and served as the control; the other was maintained on half the normal food ration for three months. During this time the underfed animals lost a considerable amount of weight, but none of them showed any signs of oedema or of any specific deficiencies. The animals were killed when the average weight of the control group was 386 g. and of the underfed group 207 g. The activity of the P-cholinesterase in each animal's serum was estimated, and the average for the control group came to 13 units (S.D. 2·04). The average for the underfed group was 12 units (S.D. 1·03) and the differences were not statistically significant. If female rats had been employed, it is probable that a different result would have been obtained, for since these experiments were made Harrison and Brown (1951) have shown that six days starvation did not reduce the P-cholinesterase in the sera of adult male rats, but did reduce from 41 units to 23 units the P-cholinesterase in the sera of adult female rats.

Experiments with Dogs

1. *The effect of various food supplements.* Seven half-starved and very thin adult dogs were obtained and fed for seven weeks on a diet which provided them with 100 Calories per kg. per day. The food consisted of brown bread, dried skimmed milk and mixed vegetables, augmented twice a week by a small allowance of meat. This ration was barely sufficient to maintain the dogs' weights. They were weighed each week and samples of blood removed for determinations of P-cholinesterase. The average results are given in Table 5.

After this preliminary stabilizing period the ration of 100 Calories was increased to 200 Calories per kg. body weight per day. Two dogs received these extra Calories as sugar, two as margarine, two as a mixture of dried skimmed milk, meat and dried fish, and one as a mixture of sugar, margarine, dried skimmed milk, meat and dried fish. The better diet was introduced gradually, but even so all dogs experienced some degree of gastro-intestinal disturbance. Several vomited, and diarrhoea was common at first. If the diarrhoea was severe the dogs were given small quantities of animal charcoal in a little warm milk by mouth. This was very effective, and by the end of the second week these troubles had been overcome; and in spite of them the body weights of all the dogs increased during the first week. The animals were maintained on the increased rations for seven weeks. Whatever the supplement, each dog gained weight rapidly and the average weight at the end of seven weeks was 7·1 kg. The general appearance of all the animals also underwent rapid improvement. At the end of the period

their coats were good and they were much more lively, but their cholinesterase activities were virtually unchanged. The mean rise of 1·2 units (Table 5) was certainly not significant, and in three of the dogs the enzyme activity was actually lower at the end than it had been at the beginning of the period.

When the dogs were taken off the special diets, they were allowed an unlimited amount of food for six weeks. A good mixed diet consisting of brown bread, dried skimmed milk, meat, and vegetables was given to each dog daily in sufficient quantity to ensure that not all of it would be eaten before the next meal time. As Table 5 shows there was no further general gain in weight, nor was there any significant change in the mean cholinesterase activity.

TABLE 5

The effect of dietary changes on the body weights and serum P-cholinesterase activities of 7 dogs

	Average values	
	Weight (kg.)	P-cholinesterase units
On arrival, half starved and very emaciated	5·0	36
After 7 weeks of further dietary restriction	4·7	36
After 7 weeks of dietary supplements	7·1	37
After a further 6 weeks of unlimited diet	7·1	37

The only previous work on this subject seems to have been an isolated experiment of Milhorat (1938) on a single dog. It was found at that time that starvation for a fortnight did not lower the serum cholinesterase, a result with which the present findings are in accord.

2. *Phosphorus poisoning.* Three normal dogs were given 10 c.c. of a 1 per cent solution of phosphorus in almond oil by stomach tube. Samples of blood were taken beforehand and afterwards at twelve-hourly intervals for two days and then daily for a further two days. The animals were all killed at the end of the experiment and post-mortem examinations were carried out. All the livers were abnormal in appearance. They appeared brittle and yellowish, and histological examination revealed moderately severe, or severe, fatty degeneration. The variations in the activity of the P-cholinesterase were greater than would have been expected in a normal dog, but were not consistently in one direction or the other. Some change had been anticipated since Steensholt and Venndt (1945) had found that chloroform poisoning raised the P-enzyme activity in the serum of dogs.

3. *Ligature of the pancreatic ducts.* Mendel and Mundell (1943) prepared cholinesterase from the pancreas of dogs and Ginsberg, Kohn and Necheles (1937) stated that the pancreatic juice from a dog contained cholinesterase in 15 times the concentration found in dog serum. Specimens of blood were

therefore taken from two normal dogs and the pancreatic ducts were ligatured under ether/Evipan anaesthesia. In one dog the operation was completely successful, and nine days later the post-mortem revealed that both lobes of the pancreas had begun to atrophy. Histological examination revealed definite but slight fibrosis with some inflammatory reaction which may have been caused by the operation. The condition of the pancreas, which was still healthy in parts, was compatible with the occurrence of complete obstruction of the ducts about 10 days before death. In spite of this the activity of the cholinesterase in the serum remained almost unchanged. It was 62 units on the day before the operation, which seems rather a high figure for a dog, and 58 units nine days after.

In the other dog the bile duct was inadvertently ligatured instead of one of the pancreatic ducts. The dog became very jaundiced and was killed a fortnight later. One of the pancreatic lobes was found to be partially atrophied and the other normal. Histological examination revealed slight but definite fibrosis of the atrophied lobe, although some parts of the tissue appeared normal. This was compatible with complete obstruction of the duct at operation. In spite of all the usual signs of obstructive jaundice the animal ate well. Samples of blood were taken prior to the operation, daily for the first five days afterwards and then on the eighth, twelfth, and fourteenth days. The P-cholinesterase activities of the corresponding sera were 28, 21, 23, 27, 23, 24, 29, 31, and 29 units respectively. Thus the activity fell slightly at first, but was certainly back at its normal level after eight days and remained there until the dog was killed. These observations were in keeping with the one made by Ginsberg *et al.* (1937), that the activity of the cholinesterase of a dog's serum was unchanged by pancreatectomy.

DISCUSSION

The evidence which has just been presented seems to leave no doubt that an insufficiency of Calories lowers the P-, and to a lesser extent the T-, cholinesterase in the serum of man. It is unlikely that a deficiency of protein, fat, carbohydrate, or any of the major dietary constituents is specifically involved. The effect of the vitamins has yet to be investigated, but if a deficiency of one or more of them was associated with a reduction in the Calorie intake a fall in the serum cholinesterase would be likely to be the result.

The present findings will remain difficult to explain until more facts have been collected. The animal experiments have not been directly helpful, for it appears that even severe undernutrition does not lower P-cholinesterase in the sera of dogs or male rats and neither phosphorus poisoning nor ligature of the pancreatic ducts in dogs has helped to explain the origin of their serum P-cholinesterase. The animal experiments, however, have been valuable in emphasizing the need for great caution in making any generalizations about cholinesterase.

A fall in serum cholinesterase has been shown to accompany liver disease in man (McArdle, 1940) and Waterlow (1950) has recently found the cholinesterase in the liver and serum of undernourished infants to rise simultaneously as their state of nutrition improved. *Sherlock and Walshe* (p. 111) found no signs of liver damage in undernourished people in Wuppertal, but unfortunately they did not measure the activity of the liver P-cholinesterase. Some change in the size or in the rate of metabolism of this organ may be responsible for the fall in the serum cholinesterase, and for the rise above normal in the grossly overfed men who had been prisoners of war in Russia. It would be most helpful to

know the source of the two cholinesterases in human serum. The two enzymes have recently been thought to be entirely separate and distinct, but since both are affected in the same way by undernutrition they may be more intimately connected than has hitherto been supposed.

It will probably take some time to solve all the problems raised by this investigation, but meanwhile there would seem to be good grounds for using the activity of the serum cholinesterase as a sensitive index of nutritional status in man. The normal range is too wide to make single determinations of much value in individual cases, but group averages have proved themselves of considerable value, and the response of individuals to treatment has been equally instructive.

SUMMARY

1. Both the "pseudo" and the "true" cholinesterase activities of the serum have been found to fall in human undernutrition and to rise again with increased food consumption. This has been shown (*a*) by comparing the mean activities of groups of people at different nutritional levels, and (*b*) by studying the effect of additional food.

2. The rise due to improved feeding was not related to the increased consumption of any of the major dietary constituents, but rather to the gradual gain in weight and well-being brought about by the better diet.

3. Undernutrition did not lower the P-cholinesterase in the sera of dogs or male rats, and its level in undernourished dogs could not be raised by dietary means.

4. Neither phosphorus poisoning nor ligaturing the pancreatic ducts appeared to alter the level of P-cholinesterase in the serum of dogs.

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XVI. THE ENZYME ACTIVITIES OF THE RED BLOOD CELLS

by AUDREY O. HUTCHINSON

A SHORT study has been made of the activities of "true" cholinesterase (Mendel, Mundell and Rudney, 1943), carbonic anhydrase, catalase, acid phosphatase, and glyoxalase in the red blood cells of men suffering from hunger oedema who were sent to the clinic in the Städtisches Krankenhaus, Barmen, in 1946. The results have been compared with those obtained from a group of normal British men who were working in Germany and eating army rations.

TECHNIQUES

Preparation of the washed cells. About 10 c.c. of blood were allowed to flow directly into a sterile bottle containing 5 c.c. of 1 per cent sodium citrate in 0·9 per cent sodium chloride solution. The mixture was then centrifuged and the supernatant fluid pipetted off. The cells were washed once with sterile 0·9 per cent saline and re-suspended in a volume of sterile saline which was usually more than once and less than twice the original volume of blood. The bottle was then filled up with liquid paraffin and stored in a refrigerator at + 4° C.

When sampling the washed cells, care was taken to avoid bacterial contamination. To obtain a uniform sample, it was found to be necessary to stir the cell suspension for at least four minutes; and this was done with a paddle-shaped stirrer, to avoid mixing the washed cells with their covering layer of paraffin. For the determination of iron 3 c.c. were taken from the bottle. The contents of each bottle were stirred and sampled at least twice on separate occasions at intervals of two or three days. Good duplicates were almost always obtained if the blood had been kept for about three months. Unless the blood had been kept for this length of time it was found to be very difficult to withdraw two similar samples.

Haemoglobin. This was estimated on the day the blood was collected by the alkaline haematin method of Gibson and Harrison (1945).

Haematocrit. Details of the method used are given on p. 401. The determinations were made on the day the blood was collected.

Iron. Iron was estimated by the method described by McCance, Widdowson and Shackleton (1936).

"True" cholinesterase. The red cell T-cholinesterase activity was estimated manometrically at 37° C. by the method of Mendel, Mundell and Rudney (1943), using 0·03 M-acetyl-β-methyl-choline chloride as substrate, but replacing sodium bicarbonate by Ringer bicarbonate (Krebs and Henseleit, 1932). For the gas phase, 5 per cent CO_2 in O_2 was used. The activities were expressed as c.mm. CO_2 per mg. Fe per min. The activities of the cholinesterases in the serum were estimated as described by *Hutchinson, McCance and Widdowson* (p. 216).

Carbonic anhydrase. The activity was measured by the boat technique (Meldrum and Roughton, 1933). The temperature was carefully controlled at 15·9 ± 0·3° C. The red cell lysate was diluted to give approximately a 1 in 200 dilution of the original whole blood, and 0·5 c.c. of lysate was used for each determination. The activities were expressed in arbitrary units per mg. Fe per min.

Acid phosphatase. The determinations were carried out by the method of King (1946). The results were expressed as mg. of phenol liberated in one hour by the volume of red cell lysate containing 10 mg. Fe.

Catalase. The activity was measured at 15·9 ± 0·3° C. in a boat apparatus, using 0·4 M-hydrogen peroxide, phosphate buffer at *p*H 6·5, and washed cell lysate diluted with distilled water to give approximately a 1 in 200 dilution of the original whole blood. According to George (1947), the reaction between catalase and hydrogen peroxide takes place in two distinct stages. The initial phase is very rapid, and the oxygen evolution is proportional to the catalase concentration. After the first 20 seconds, the activity falls: the evolution of gas continues, but at a slower rate. The mechanism of this change is not fully understood, but it is thought probably to be due to some alteration in the enzyme brought about by its substrate. For the purposes of this work, the rate of oxygen evolution over the first 20 seconds was measured, and, under the conditions specified above, this varied directly with the catalase concentration in the sample. The activities were calculated in arbitrary units per mg. Fe per min.

Glyoxalase. The activity was measured manometrically in a Barcroft apparatus at 37° C., using excess of methyl glyoxal as substrate, Ringer bicarbonate buffer and excess of glutathione as coenzyme. The gas phase consisted of a mixture of 5 parts of carbon dioxide and 95 parts of oxygen by volume. The results were expressed in c.mm. CO_2 per mg. Fe per min.

Effect of Storage

The cells were stored for some months before the estimations were made, but this does not seem to reduce the activities of these enzymes. Keilin and Wang (1947) have shown that the erythrocyte enzymes carbonic anhydrase, catalase, glyoxalase, and cholinesterase retain their full activities for many years if kept under sterile anaerobic conditions at 0° C. No direct experiments have been made to prove the stability of these enzymes, but no evidence of loss of activity has been found, for:

(*a*) The activities of catalase, phosphatase, glyoxalase, and T-cholinesterase which were recorded on the stored cells corresponded well with those obtained on fresh samples of washed cells.

(*b*) The activities of phosphatase and T-cholinesterase were within the normal limits reported by other workers (King, 1946; Mendel *et al.*, 1943).

(*c*) T- and P- ("pseudo") cholinesterases do not lose their activity in serum if kept for periods of up to twelve months.

Since, moreover, the aim of this work was to compare the enzyme activities found in normal and undernourished subjects' red blood cells, and since the two series of washed cells were kept for the same length of time under exactly the same conditions, any deleterious effects of storage, which must in any case have been small, could be disregarded.

RESULTS

Most of the undernourished subjects were slightly anaemic, for their haemoglobin averaged 12·5 g. per 100 c.c. of blood while the average for the controls was 16·0 g. per 100 c.c. The haematocrits of the undernourished group averaged 39·5 per cent, while those of the controls averaged 48·9 per cent. The ratio haematocrit/haemoglobin in the two series was virtually identical, being 3·12 for the normals and 3·15 for the undernourished. Hence, any given volume of cells in either series contained on average the same amount of haemoglobin. The enzyme activities have therefore been calculated per mg., or per 10 mg., Fe.

TABLE 1

Comparison of the serum and red cell enzymes in normal and undernourished subjects

			Serum		Cells				
	Haemoglobin (g./100 c.c.)	Haematocrit (per cent)	P-cholinesterase (c. mm. CO_2/ c.c./min.)	T-cholinesterase (c. mm. CO_2/ c.c./min.)	T-cholin-esterase (c. mm. CO_2/ mg. Fe/min.)	Carbonic anhydrase (units/mg. Fe/min.)	Phosphatase (mg. phenol/ 10 mg. Fe/hr.)	Catalase (units/mg. Fe/min.)	Glyoxalase (c. mm. CO_2/ mg. Fe/min.)
Normals (13 subjects)									
Average ..	16·0	48·9	73·4	1·001	49·6	36·7	45·3	28·3	4,860
Range ..	13·6—17·2	45·1—53·0	59·2—99·4	0·720—1·210	23·1—70·8	22·1—48·6	19·8—63·5	9·7—38·0	960—7,490
S.D. ..	0·51	2·23	11·2	0·142	15·2	7·5	12·7	8·7	1,660
Undernourished (23 subjects)									
Average ..	12·5	39·5	42·4	0·773	54·1	43·2	50·8	22·5	5,720
Range ..	8·6—16·3	31·7—47·5	25·8—65·7	0·285—1·210	21·6—74·4	11·2—80·0	28·1—119·0	3·5—32·6	1,960—12,000
S.D. ..	2·01	2·35	12·9	0·165	13·1	18·5	18·1	6·9	2,720

The average results of haemoglobin and haematocrit estimations, and the average activities of each of the enzymes measured, are shown with their respective ranges and standard deviations in Table 1. The difference in average serum cholinesterase activity between normal and undernourished individuals is obvious, and has been discussed elsewhere (*Hutchinson et al.*, p. 216), but the serum cholinesterases have been included in the Table in order to emphasize that undernutrition has a different effect upon the enzymes of the serum and those of the cells.

When the two sets of data for the cell enzymes were compared, the only difference which was found to be statistically significant was that catalase was lower in the undernourished men ($t = 2{\cdot}14$; $P = 0{\cdot}05$), and the following test suggests that this difference may not have any biological meaning. The undernourished subjects were divided into two sub-groups on the basis of the levels of their serum P-cholinesterases (Table 2). The 12 with the lower serum activities were considered to be the most undernourished, and this was supported by the finding that they also had lower serum proteins, serum T-cholinesterases, haematocrits, and haemoglobins. The serum T-cholinesterases and haematocrits were both significantly different ($t = 3{\cdot}41$; $P = <0{\cdot}01$ and $t = 2{\cdot}47$; $P = 0{\cdot}02$—$0{\cdot}05$ respectively). The "more" undernourished sub-group, however, had a higher mean activity for cell catalase than the "less" undernourished sub-group (24·7 as against 20·2 units), so that the level of cell catalase may not really be a reflection of nutritional status. The mean carbonic anhydrase activity of the "more" undernourished sub-group was 51·6 units, significantly higher than the figure for the normal group ($t = 3{\cdot}30$, $P = <0{\cdot}01$). This would be a point to bear in mind if further work was being undertaken on the relationship between nutritional status and the activities of the enzymes in the red blood cells, but the difference may have no biological meaning, for the average carbonic anhydrase activity of the "less" undernourished sub-group was 34·1 units, which was slightly lower than the normal average of 36·7.

Enzyme Relationships

An attempt was made to determine whether the concentrations of the enzymes in the red blood cells bore any relation to each other. Every cell enzyme activity for each man's red blood cells was compared with the average for the series. Of the 13 normal subjects, 7 had red cell enzyme activities that were all greater or all less than the respective averages. This was greater than the number expected to occur by chance, but the same tendency was not shown in the undernourished men. Here, out of 23, only 5 had red cell enzymes all greater or all less than the average, and this was less than the expected number. In view of the small number of subjects, the evidence was not strong enough for any conclusion to be drawn.

SUMMARY

1. Undernutrition, even if fairly severe, probably does not raise or lower the activities of T-cholinesterase, phosphatase, catalase, or glyoxalase in the red blood cells. There was some evidence of a slight increase in the carbonic anhydrase activity in the most undernourished subjects.

2. No changes were found in the cell enzymes comparable in magnitude or interest with the fall in the activities of P- and T-cholinesterase which occurs in the serum in undernutrition.

TABLE 2

Evidence of undernutrition in "more" and "less" undernourished groups

	Normal average	"Less" undernourished		"More" undernourished	
		Average	Percentage below normal	Average	Percentage below normal
Whole Blood:					
Haemoglobin (g./100 c.c.)	16·0	12·9	19·4	12·2	23·7
Haematocrit (per cent) ..	48·9	41·6	14·9	37·4	23·5
Serum:					
Proteins (g./100 c.c.)	6·96	5·76	17·3	5·42	22·2
Albumen (g./100 c.c.)	4·81	3·62	24·8	3·24	32·7
Globulin (g./100 c.c.)	2·06	2·20	Nil	2·19	Nil
A/G Ratio	2·345	1·745	25·6	1·462	37·7
T-cholinesterase (c. mm. CO_2/c.c./min.) ..	1·001	0·956	4·5	0·608	39·2
P-cholinesterase (c. mm. CO_2/c.c./min.) ..	73·4	53·4	27·3	32·9	55·2

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XVII. SEDIMENTATION RATES

by Lois A. Thrussell and R. A. McCance

Mollison (1946, and personal communication) determined the erythrocyte sedimentation rate of 28 of the people found in the concentration camp at Belsen. He used Wintrobe's method. The sedimentation rates were all very high, and even after all persons with tuberculosis had been excluded, and also those suspected to have had typhus in recent months, the sedimentation rates of the remaining seven patients averaged 45 mm. in the first hour. The average haematocrit of these patients was 35 and their serum contained 6·7 per cent of protein. Mollison concluded that a high sedimentation rate was characteristic of starvation, whether or not infection was present and apart altogether from the accompanying anaemia. Adelsberger (1946) reported from memory some average sedimentation rates and serum proteins which had been determined in Auschwitz concentration camp. The sedimentation rate increased very much as the state of nutrition deteriorated and the serum proteins correspondingly fell. Patients with tuberculosis and obvious infections were excluded, but practically all the inmates of the camp were infected with lice and scabies, and the results given may not have all the significance assigned to them. Leyton (1946) compared the state of nutrition of British and Russian prisoners of war at a camp near Tost in Eastern Germany. The basal daily diet supplied by the camp authorities consisted of 330 g. of bread, 400 g. of potatoes, 400 g. of vegetables, 25 g. each of fat, sugar, jam, and meat, and 15 g. of meal. This provided about 1,600 Calories per day and was the only food received by the Russian prisoners. The British received Red Cross parcels, which provided another 1,300 Calories per day. Leyton found that the British were adequately nourished and that they had normal erythrocyte sedimentation rates (Westergren's method). The Russians deteriorated steadily on the food supplied, and Leyton noted that less than 5 per cent of them had sedimentation rates within normal limits. Even when the serum proteins were still normal, the falls averaged 25 mm. in the first hour and 51 mm. in the second, and when the serum contained less than 4 per cent of protein the falls averaged 79 mm. for the first and 106 mm. for the second hour. Leyton drew the conclusion that "the increase in the sedimentation rate is probably the first sign that the body is not receiving sufficient nourishment; but the reason for the rapid fall of the red cells in undernourishment is obscure, and no reference has been made to it in previous publications outside Russia". Against this must be set the fact that Simonart (1945) found the sedimentation rates to be quite normal in the undernourished inmates of Belgian prisons during the German occupation.

PRESENT INVESTIGATION

Erythrocyte sedimentation rates were determined by Westergren's method in a series of civilians admitted to the Städtisches Krankenhaus, Barmen, for nutritional investigation in 1946. A few of these were found to have raised sedimentation rates, but there was often an obvious cause such as tuberculosis or nephritis. After excluding such patients and all those who were not at least 12 per cent below the expected weight for their height and age according to the Hassing-Schall Tables, a group of 45 men and 3 women remained. The majority of these had oedema, and all were in a bad nutritional state. Only two of the men had sedimentation rates greater than 15 mm. in the first hour. One of these

TABLE 1

The sedimentation rates, serum proteins and haemoglobin concentrations of undernourished people

Subject No.	Percentage underweight	Serum protein (g./100 c.c.)	Oedema grading	Haemoglobin (g./100 c.c.)	Erythrocyte sedimentation (mm.)	
					1 hour	2 hours
B 5	36	4·90	1	12·3	14	30
B 8	20	6·96	3	11·2	9	24
B 26	13	5·08	2	14·9	2	5
B 35	27	5·88	0	13·1	5	10
B 37	14	4·25	4	10·9	5	10
B 40	11	4·66	4	11·6	3	8
B 42	19	5·30	2	14·1	5	11
B 44	11	5·55	2	14·0	4	10
B 45	20	5·45	2	13·2	2	6
B 46	26	5·71	2	11·5	5	13
B 48	23	6·20	2	13·8	4	9
B 49	14	5·37	2	11·8	5	12
B 52	32	5·76	0	16·3	7	22
B 53	30	5·60	2	12·6	18	38
B 54	17	6·08	0	11·8	10	27
B 55	25	6·05	1	12·3	7	16
B 57	3	5·50	2	12·8	7	20
B 59	25	4·75	2	10·3	6	14
B 62	17	5·12	3	14·8	4	11
B 65	25	—	1	13·0	2	5
B 66	13	5·40	2	13·3	5	11
B 68	20	6·65	0	14·5	2	5
B 69	29	5·92	0	13·8	9	19
B 70	38	6·55	0	11·4	6	11
B 71	20	6·58	0	12·3	9	21
B 72	25	6·02	2	13·3	4	11
B 74	11	5·72	2	12·6	4	10
B 76	15	4·56	3	13·5	9	20
B 77	13	4·69	4	10·5	4	8
B 78	23	4·98	3	10·6	8	22
B 79	35	5·25	3	9·4	13	41
B 80	16	6·00	2	13·9	4	11
B 81	26	6·29	4	9·6	4	8
B 84	19	5·85	2	12·3	15	40
B 85	15	5·63	0	13·2	12	28
B 87	20	5·12	4	10·6	10	25
B 90	17	6·20	2	13·5	13	45
B 91	17	6·80	2	16·1	3	5
B 93	18	5·95	2	13·6	9	28
B 94	38	6·90	2	12·7	10	34
B 97	28	6·15	0	12·6	14	42
B 100	17	5·43	3	10·8	9	26
B 111	22	5·48	3	14·5	4	10
B 113	19	6·72	2	14·5	4	12
B 116	22	6·32	0	14·1	7	12
Average	21	5·71	—	12·7	7	18

had a boil and the other chronic bronchitis. None of the women had sedimentation rates greater than 20 mm. in the first hour. Todd and Sanford (1943) give 15 and 20 mm. as the upper limits of normality for Westergren's method for men and women respectively. The falls for the men averaged 7·4 mm. for one and 17·9 mm. for two hours and the details are given in Table 1. It will be seen that many of the patients with low serum proteins had also low sedimentation rates, e.g. B37, B40, and B59, while one patient, whose massive oedema just excluded him from Table 1 by maintaining his body weight at a falsely high level, had only 3·58 per cent of protein in his serum, but his sedimentation rate was 4 mm. in the first hour and 8 mm. in the second.

The present results do not throw any doubt upon Mollison's findings, and his patients had lost so much more weight and were in any case so different from those seen at Wuppertal that his conclusions may be quite correct. The figures given by Leyton were obtained as part of a well-controlled investigation, and there can be no reasonable doubt that the high rates found among the Russians were correct. The present results, however, which confirm those of Simonart (1945), do show that Leyton's conclusions were probably wrong, for it is clear that undernutrition *per se*—as met with in Wuppertal—did not raise the sedimentation rate. Indeed, when cognizance is taken of the fact that one or two of these people may have been suffering from undetected infections, and that many of them were slightly anaemic, it is surprising that the sedimentation rates were on the whole so normal. It may be added that the present findings are in complete agreement with local German experience, for Schulten (1946) obtained exactly the same results at Köln, and in the Barmen hospital a patient was not generally considered to be suffering from uncomplicated undernutrition unless he had a normal sedimentation rate.

SUMMARY

Sedimentation rates were generally found to be normal in civilians suffering from uncomplicated undernutrition.

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XVIII. PROTHROMBIN TIMES

by M. D. Newman and P. R. V. Tomson

Since it is known that the serum proteins are lowered in many undernourished persons, and since it had been found that the cholinesterase might also be considerably reduced even when the serum proteins were normal, it was decided in the summer of 1947 to compare the concentrations of prothrombin found in the blood of healthy and of undernourished persons. A few of those attending the out-patient clinic had been noted to have small subcutaneous haemorrhages, but there had been no clinical evidence of prothrombin deficiency. In 1945 and 1946 Walters, Rossiter and Lehmann made some estimations of prothrombin in the plasmas of repatriated Indians who had been prisoners of the Japanese and obtained results within the normal range.

METHOD

The method used was that of Quick (1939). The thromboplastin was prepared as follows: a rabbit's brain was extracted with acetone and aliquots of the extract were placed in small tubes and dried at a temperature below 0° C. The tubes were then sealed. When estimations were to be made, 4 c.c. of normal saline were added to one of these tubes; the suspension so formed was allowed to settle for five minutes, after which the cloudy supernatant fluid was removed with a pipette and used as such. Since the strengths of the thromboplastin suspensions were not constant, the clotting time of P.T.'s plasma was determined whenever estimations were being made. The times for all other plasmas were compared with the time for P.T.'s plasma and then scaled up or down on the assumption that P.T.'s clotting time had been 20 seconds.

SUBJECTS

Fifty-three undernourished men were selected from those attending the clinic at Barmen hospital. Some were civilians and some were prisoners of war repatriated from Russia. A group of them had been under investigation for about a year and had been given an excellent diet for two months in the autumn of 1946 (*Widdowson*, p. 313). They had deteriorated considerably since then, but were better nourished than they had been in the summer of 1946. The 53 subjects were 9 to 27 per cent (average 18 per cent) below their former weights, and their serum proteins ranged from 5·5 to 8·4 per cent. Twenty-five of them had oedema. Nine British soldiers and six male members of the Unit acted as the controls.

RESULTS

The average clotting time of the 53 undernourished subjects was 20·4 seconds (S.D. 2·2): five of the "times" were over 23 seconds. There was no correlation between the level of plasma proteins and the prothrombin time. The average clotting time of the 15 normal subjects was 21·1 seconds (S.D. 0·9): one figure was over 23 seconds. The histograms of the results of the two groups are shown in Fig. 1.

If Quick's method be taken as giving a true estimation of the concentration of prothrombin in plasma, these results show that the level of prothrombin does not fall in the type and degree of undernutrition seen in Wuppertal in 1947. This statement is true of both the prisoners of war and the civilians. It is possible

that the clotting time may be prolonged in severe undernutrition when and if the serum proteins have fallen to a very low level, but it would seem that prothrombin is not one of the serum proteins to show an early fall—as cholinesterase appears to be. These results are in keeping with those of Walters, Rossiter and Lehmann.

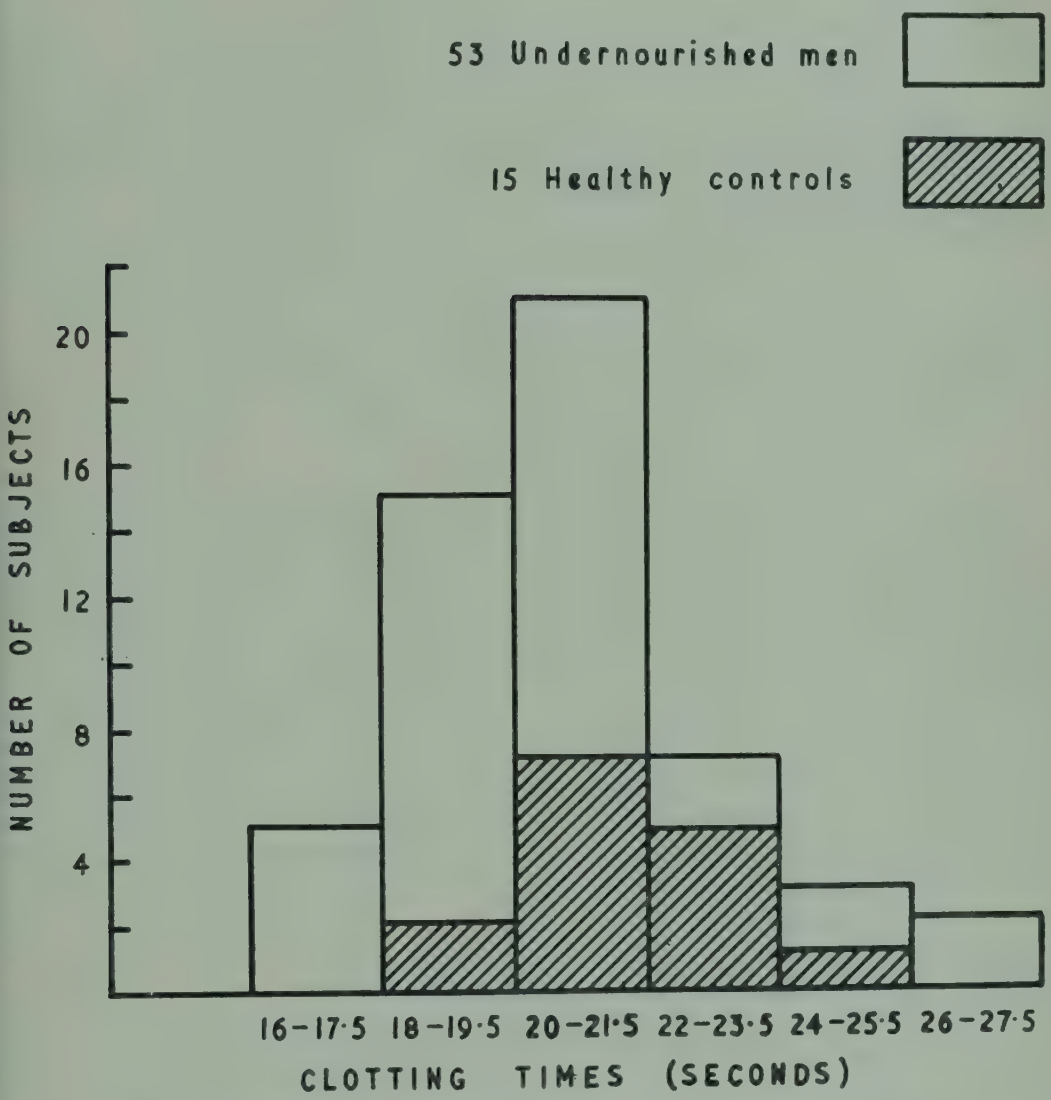

FIG. 1. Histogram showing frequency distribution of prothrombin times

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XIX. THE EXCRETION OF DIASTASE IN THE URINE OF UNDERNOURISHED PERSONS

by E. M. GLASER

A GROSS increase of diastase in the blood and urine is usually a sign of acute pancreatitis, and the determination of serum and urinary diastase is recognized to be of considerable value in the differential diagnosis of this disease. Perakis and Bakalos (1943), however, recorded very high diastase values in the serum of persons suffering from undernutrition. They did not, unfortunately, state the method employed for their investigation or the total number of persons examined by them, and they tabulated only a few selected results.

Diastase is freely excreted by the kidneys, and estimations of urinary diastase give a good indication of the levels of enzyme in the serum. It is, in fact, more usual to determine diastase in the urine than in the serum, and it was decided to check the conclusions of Perakis and Bakalos by doing so.

SUBJECTS AND METHODS

Ten undernourished men were investigated. Twenty-four-hour samples of urine were collected under toluene and stored on ice. The estimations were usually carried out at once and were always completed within 48 hours. King's (1946) method was used, with these modifications: (1) Additional dilutions of 1 to 15 and 1 to 30 were prepared in the following manner: 1 c.c. of the 1 to 5 dilution of urine was mixed with 2 c.c. of buffer solution giving a dilution of 1 to 15; 1 c.c. of this was mixed with 1 c.c. of buffer solution, giving a dilution of 1 to 30. (2) A 2 per cent solution of starch was prepared as described by Harrison (1937), and a 0·2 per cent solution was made up from this each day. (3) The urine of subject B88 contained less than 5 Wohlgemuth Units per c.c., and a second estimation was made with the lower range of dilutions and an additional dilution of 1 to 2·5. This was prepared by mixing 2 c.c. of urine with 3 c.c. of buffer solution.

TABLE 1

The excretion of diastase in the urine of undernourished persons

Subject No.	Urine volume (c.c./24 hr.)	Diastase (Wohlgemuth units) per c.c. urine	per 24 hr.
B 87	3,050	10·0	30,500
B 88	1,680	2·5	4,200
B 90	2,150	5·0	10,750
B 93	1,910	10·0	19,100
B 95	2,920	5·0	14,600
B 97	2,750	5·0	13,750
B 99	1,710	10·0	17,100
B 103	2,110	15·0	31,650
B 107	2,650	10·0	26,500
B 110	2,500	5·0	12,500

RESULTS

The results are shown in Table 1. According to Harrison (1937) the normal output of diastase in the urine is 8,000 to 30,000 Wohlgemuth Units in 24 hours. The results were within this range, except those of B88, which were lower. The present findings, therefore, do not confirm the claims of Perakis and Bakalos (1943).

SUMMARY

1. Ten undernourished men were found to be excreting normal, or, in one case, subnormal quantities of diastase in the urine.

2. No evidence was found in favour of the claims of Perakis and Bakalos (1943) that the serum of undernourished people contains large amounts of diastase.

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XX. CARDIAC OUTPUT AND THE PERIPHERAL CIRCULATION

by SHEILA HOWARTH

DURING and after the 1914-18 war, a syndrome characterized by bradycardia, oedema, and often a fall in blood pressure was described in Europe (*McCance*, p. 21). So far as they concerned the heart and circulation these descriptions were mainly clinical, since detailed studies of the circulatory dynamics were impossible by the methods then available. A similar syndrome has been described during and since the recent war. During the German occupation of Belgium, Govaerts and Lequime (1942) studied persons with oedema, bradycardia and normal blood pressures. The peripheral venous pressure was within normal limits; the arm-tongue circulation time was increased and there was a striking reduction in the basal metabolic rate. The cardiac output, measured by the acetylene method, was considerably reduced, and the arteriovenous oxygen differences were increased. In Germany, Landes (1943), working with a "pulse wave velocity" method on three subjects with slow heart rates and normal blood pressures, calculated that the arteriovenous oxygen differences were relatively normal, and found an increased stroke volume and a decreased cardiac output. In a further twelve cases Landes and Arnold (1947) found variations from 32 to 80 c.c. per litre in the arteriovenous oxygen differences, but the cardiac output was, with two exceptions, diminished. In Holland, Cardozo and Eggink (1946) found an increased circulation time, but no venous engorgement, in persons with bradycardia and systolic blood pressures below 100 mm. Hg. In Germany Heilmeyer (1946) attempted to divide cases of oedema into two groups. The patients in one group had tachycardia, low blood pressure and enlargement of both sides of the heart. They were found to have an increased circulation time and an increased blood volume, and were diagnosed as cases of vitamin B_1 deficiency. The patients in the other group, who were stated to be suffering from a true albumen-deficiency oedema, had slow pulse rates.

The problem of undernutrition was studied experimentally on 34 male volunteers in America (Keys, 1946a, b; Keys, Taylor, Mickelsen and Henschel, 1946; Keys, Henschel and Taylor, 1947). The subjects developed profound bradycardia, a small decrease in blood pressure, and oedema. Peripheral venous pressure fell by an average of 5 cm. of water during the period of semi-starvation. An attempt was made to calculate the cardiac output from roentgen-kymographs, and the figures were reported as being below the normal values described for this somewhat unsatisfactory method. Skin temperatures fell, and cyanosis of the nailbeds was noted in all subjects.

The studies now being reported were made during July and August, 1946, by methods which were at that time in use at the British Postgraduate Medical School.

SUBJECTS

The subjects were admitted to the Barmen Hospital from the out-patient clinic. They were not intended to represent a cross-section of the population or even of the patients attending the clinic, but were selected because they showed some of the circulatory changes stated to be due to undernutrition. All had bradycardia and either had oedema on admission to hospital (Table 1) or gave a history of recent oedema. About half the cases were selected because their blood pressures were unusually low. An attempt was made to exclude

patients with valvular lesions, sepsis, anaemia or thyrotoxicosis, as well as those giving a history of cardiac decompensation or ischaemia. No one was selected as a subject if he was over the age of 70. The series included only two women, for few women were attending the clinic at that time and they usually refused to be admitted for domestic reasons. All the subjects had been receiving the basic food ration of 1,050 Calories per day, supplemented no doubt in many instances from other sources (*McCance and Widdowson*, p. 1). Four men had supplementary rations as heavy workers and two as moderately heavy workers. Three had received extra food on account of hunger oedema.

Though all the subjects complained that they were tired and unwilling to exert themselves, only two on close questioning admitted breathlessness on exertion (*Davis*, p. 147), and one of these two said that it occurred only after considerable effort. The other, B80, also gave a history of several attacks of nocturnal dyspnoea and was later found to have had a systolic blood pressure of 240 mm. Hg before the war. There were no complaints of anginal pain. Many complained of coldness, numbness and occasional tinglings of the extremities, but the fingers were not described as going "blue" or "white". All had been suffering from nocturnal frequency and polyuria.

Loss of weight, over 10 kg. in all subjects except one, was obvious from the sunken eyes, the sharply outlined temporal crest, the wasted buttocks and the folds of loose abdominal skin. The patients were apathetic, and answered questions slowly though correctly. They tended to move slowly and some were observed to become abnormally breathless on climbing stairs. Their hair, eyebrows and skins were all normal. The thyroid gland was impalpable except in one subject, in whom the isthmus alone could be felt. With two exceptions, their resting heart rates were below 60 beats per minute. One of the two exceptions was discovered to have a raised sedimentation rate of unknown aetiology (B10), and the other (B91) to have urethritis. Their systolic and diastolic blood pressures were labile and some of them varied by about 30 mm. Hg from day to day. Systolic blood pressures above 150 mm. Hg were uncommon, not only in this recorded series but also among clinic patients, many of whom at that time had systolic blood pressures below 110 mm. Hg. This was noted in Germany after the 1914–18 war (Fishberg, 1939) and was also seen in Holland during the German occupation (Lups and Francke, 1947). The blood pressure was usually lowest on admission to hospital and rose with rest in bed, as it did in cases studied in Belgium (Govaerts and Lequime, 1942). In about half the subjects the jugular venous pressure as judged by Lewis's method (Lewis, 1946) was observed to be raised to the level of the sternal angle or above it. The apex beat was often impalpable, and in such cases an attempt was made to estimate the size of the heart by percussion. The heart sounds were always clearly audible and sinus rhythm was detectable.

The extremities were pink and moderately warm, and did not resemble the cold cyanotic hands seen in myxoedema or described by others in undernutrition (Keys, 1946a; Keys *et al.*, 1947). Capillary pulsation was occasionally detectable in the nailbeds. The external temperatures varied considerably during the weeks in which these observations were made, but the rooms were never cold.

METHODS

Cardiac Catheterization

The method used was that described by Cournand and Ranges (1941) and McMichael and Sharpey-Schafer (1944a), with certain modifications made

necessary by the lack of X-ray control. The catheter was introduced through the median basilic vein into the superior vena cava or right auricle. Deviation up the internal jugular vein was detected by a "Queckenstedt" test; that is, if pressure at the root of the neck produced a rise of pressure in the saline manometer the catheter was assumed to be in the veins of the neck. It was then manipulated into the right ventricle, where its position was recognized by the size and character of the pulsations and by the record of a pressure higher than clinical observations of the veins of the neck would have led one to expect. An additional guide was obtained from the extrasystoles which are sometimes produced by the presence of a catheter in the right ventricle. The catheter was then slowly withdrawn until the sudden diminution of pulsations and the sudden fall in pressure indicated that the tip lay in the auricle just above the tricuspid valve. Measurements of right auricular pressure and samples of mixed venous blood were taken from this position. Arterial samples were obtained from the brachial artery at either the beginning or the end of the observations. At the end of the tests oxygen consumption was measured with a Knipping apparatus. Blood for haemoglobin estimation was taken from the right auricle and the oxygen unsaturation of the blood samples was estimated in a Haldane blood gas apparatus. Mean pressure was assumed to be half the sum of the systolic and diastolic blood pressures. Total peripheral resistance was calculated in arbitrary units from the formula

$$\text{total peripheral resistance} = \frac{\text{mean blood pressure (mm. Hg)}}{\text{cardiac output (l./min.)}}$$

and the results were expressed as a percentage of normal values (Table 1).

All the subjects had been resting in bed for at least two hours before the observations were made, and lay supine during the tests with the trunk at an angle of 30° with the horizontal. Rapid infusions of normal saline or isotonic glucose were given through the catheter to raise right auricular pressure. The antecubital veins of the opposite arm were used for venesection. Cuffs placed on the thighs and inflated to a pressure just below diastolic blood pressure were used to decrease right auricular pressure (Ebert and Stead, 1940; McMichael and Sharpey-Schafer, 1944a, b). Atropine was given intravenously in the doses shown in Table 3. "Exercise" lasted for three minutes and consisted of rapid dorsi- and plantar-flexion of both feet against resistance while the knees remained extended.

Peripheral Bloodflow

Hand and forearm bloodflows were measured by the modified Lewis-Grant plethysmograph (Barcroft and Edholm, 1943). The temperature of the water bath was 34° C. (Barcroft and Edholm, 1946). The subjects rested for at least two hours before the tests and sat upright in a chair while the tests were in progress. They were kept comfortably warm and care was taken to prevent the brachial artery being compressed by the side of the bath. Measurements of the blood pressure were made on the opposite arm. In the heating experiments, the legs were immersed to just below the knee in a water bath at temperatures ranging from 43·5 to 45·3° C., according to the tolerance of the subject, and heating was continued until there was free sweating and capillary pulsation was easily seen in the tissues under the nails.

TABLE 1

General data

Subject No.	Age and Sex	Height (m.)	Weight (kg.) Present: Previous	Basal metabolic rate (% normal) (2 estim.)	Pulse (beats/min.)	Blood pressure (mm. Hg)	Mean R. ventricular pressure (cm. saline above sternal angle)	Mean R. auricular pressure (cm. saline above sternal angle)	Arterio-venous O_2 diff. (c.c./l.)	Cardiac output (l./min.)	Oxygen consumption (c.c./min.)	Total peripheral resistance (% normal)	Oedema grading	Remarks
B 10	51 F	1·52	34·5 73·0	−11 −11	98	100/70	+5·5	−2·5	43·7	3·6	156	118	2	Raised E.S.R. ? cause
B 26	26 M	1·80	64·4 —	−22 −17	56	93/67	+4·0	−4·5	43·0	4·5	192	85	1	
B 30	48 M	1·70	63·5 77·5	−9	54	90/65	+2 0	−3·0	41·7	5·3	222	74	2	
B 36	50 M	1·71	64·6 80·0	−13 −6	38	106/76	+9·0	+3·5	49·0	4·6	230	99	0	
B 37	64 M	1·59	54·0 80·0	−12 −8	42	150/90	+7·0	± 0	36·8	4·5	166	133	4	
B 64	48 M	1·69	69·0 79·0	−27 −22	40	118/82	+6·0	−2·0	42·2	4·8	200	105	1	
B 65	54 M	1·72	55·0 77·0	−13 −17	52	128/90	+3·0	−2·5	38·3	5·2	198	101	0	
B 70	61 M	1·79	49·0 77·5	−19 −20	48	96/72	+2·0	−3·5	48·7	4·3	208	98	0	
B 74	32 M	1·80	68·0 —	−18 −21	52	89/56	+4·5	± 0	41·4	6·1	250	60	2	
B 75	54 F	1·68	49·0 88·0	−9 −15	64	127/79	+5·5	−8·5	27·6	7·5	208	69	3	
B 76	44 M	1·70	60·0 72·5	−24 −29	52	94/64	+3·0	−2·5	40·7	5·0	202	80	3	
B 78	66 M	1·62	50·0 77·5	—	60	130/66	+4·0	−5·0	47·1	5·1	238	96	3	Multiple extrasystoles
B 79	56 M	1·68	45·0 66·0	−21 −22	50	130/78	+2·0	−4·5	62·5	2·9	178	178	3	
B 80	59 M	1·75	63·0 118·0	−18	56	112/62	+0·5	−5·0	39·8	4·5	180	97	2	B.P. 240/– before 1939
B 83	53 M	1·72	67·5 78·0	−24	52	106/64	+4·5	−2·0	40·8	4·1	168	104	5	
B 85	54 M	1·73	62·0 90·0	−13 −16	48	120/88	−2·0	−6·0	56·9	3·2	180	162	0	
B 88	48 M	1·70	59·7 79·5	—	60	94/70	+5·5	−5·0	38·0	5·2	198	79	3	
B 90	54 M	1·63	54·0 87·0	−6	52	112/65	+2·5	−5·5	36·3	7·1	255	87	2	
B 91	46 M	1·63	54·0 70·0	−8	66	144/85	+7·0	−5·0	41·1	5·3	218	110	2	Urethritis
B 92	55 M	1·68	63·5 90·0	−5	46	140/80	+8·5	+2·0	39·5	6·0	237	95	3	

RESULTS

Cardiac Catheterization

General data. The age, sex, height, weight and basal metabolic rate of each of the 20 subjects studied are given in Table 1. This table also gives the mean right auricular and right ventricular pressures, the arteriovenous oxygen difference, the oxygen consumption and the cardiac output for each subject, and the blood pressure and heart rate at the time these observations were made.

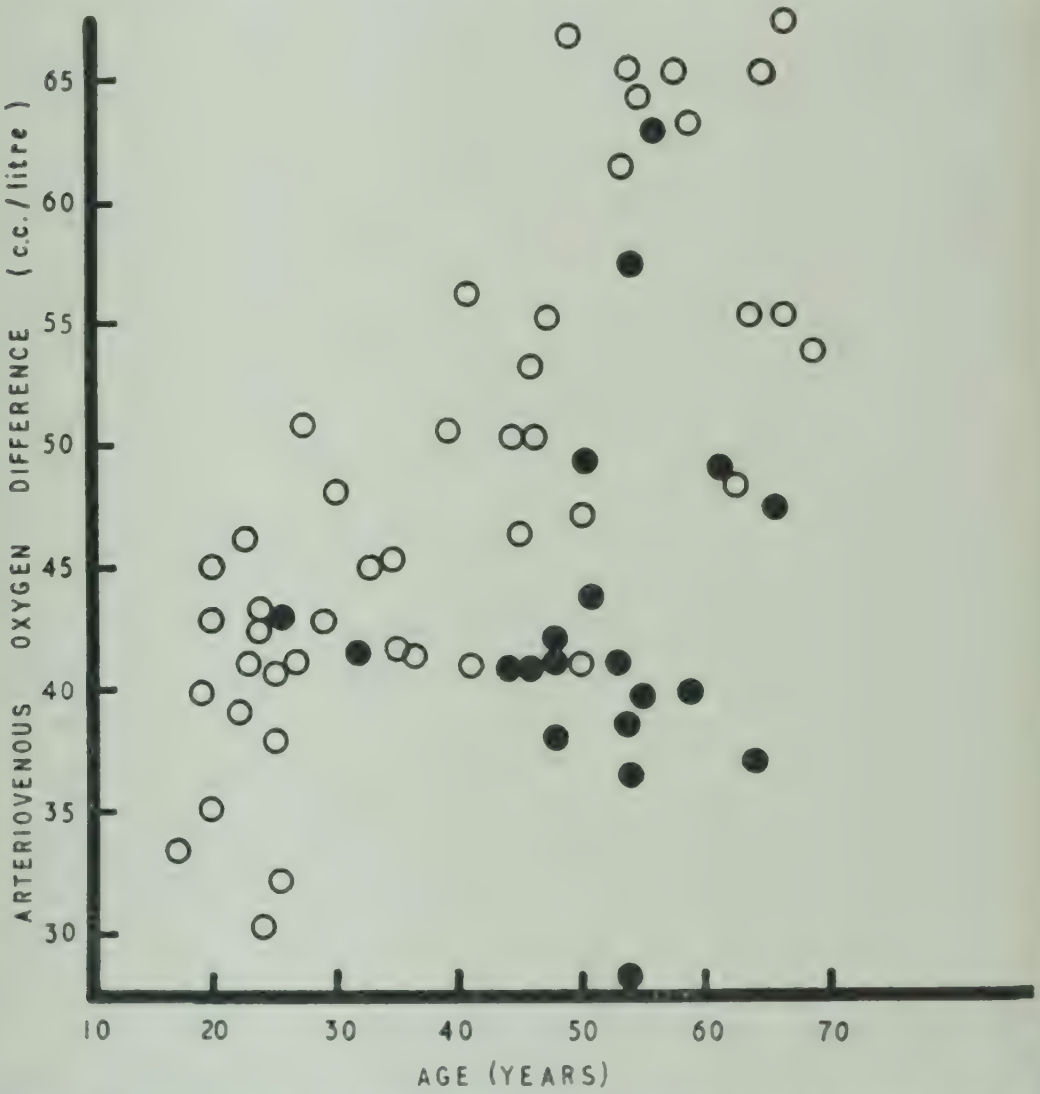

FIG. 1. Diagram showing that arteriovenous oxygen difference tends to increase with age in normal subjects (clear circles). The black dots represent undernourished subjects, and in these the arteriovenous difference tends to be decreased.

It will be seen that the auricular pressure, oxygen consumption and cardiac output varied considerably. Eleven of the right auricular pressures were above the upper limits of normal for subjects lying in this position (−4 cm. saline relative to sternal angle level). Nine of them were within normal limits. Seventeen of the differences between the mean right auricular and the mean right ventricular pressure were less than 10 cm. of saline. The cardiac output at rest was generally within the normal range which is 4–6 litres per min. One value was just over 6, and two were over 7 litres per min.: two were between 3 and 4, and

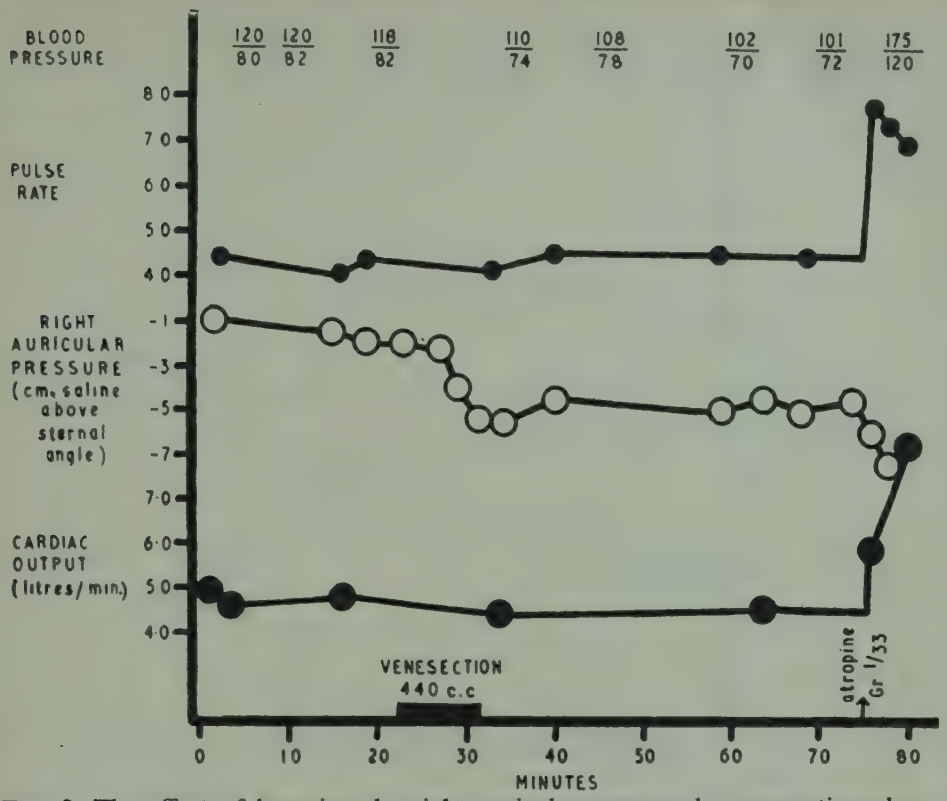

FIG. 2. The effect of lowering the right auricular pressure by venesection alone (Subject B 64).

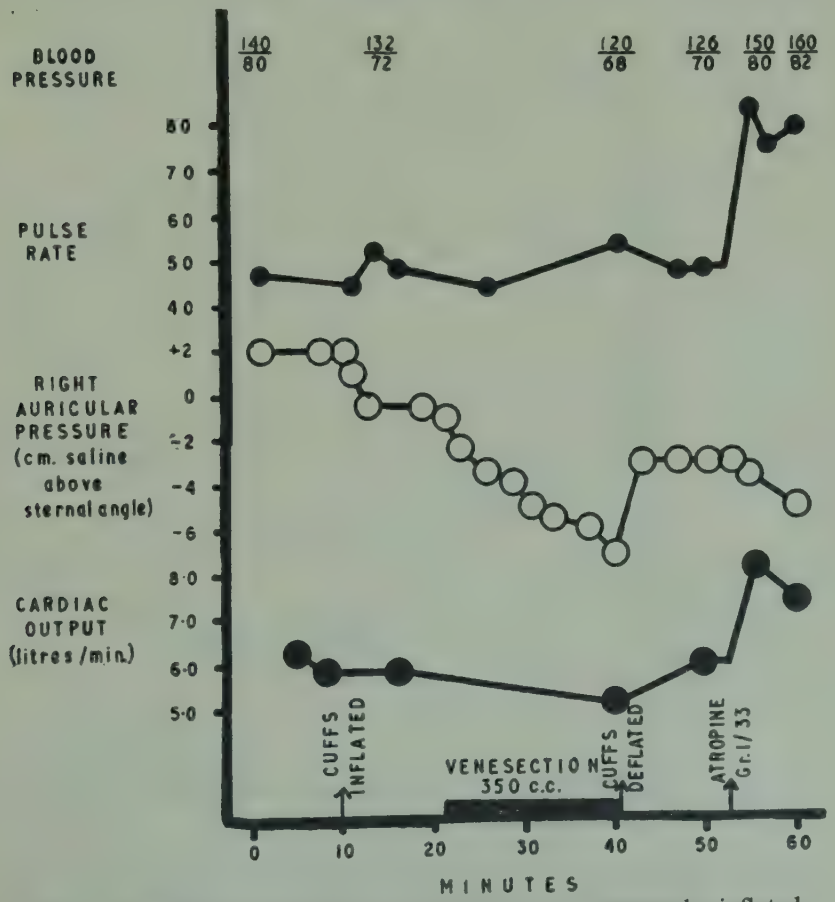

FIG. 3. The effect of lowering the right auricular pressure by inflated cuffs on the legs and venesection (Subject B 92).

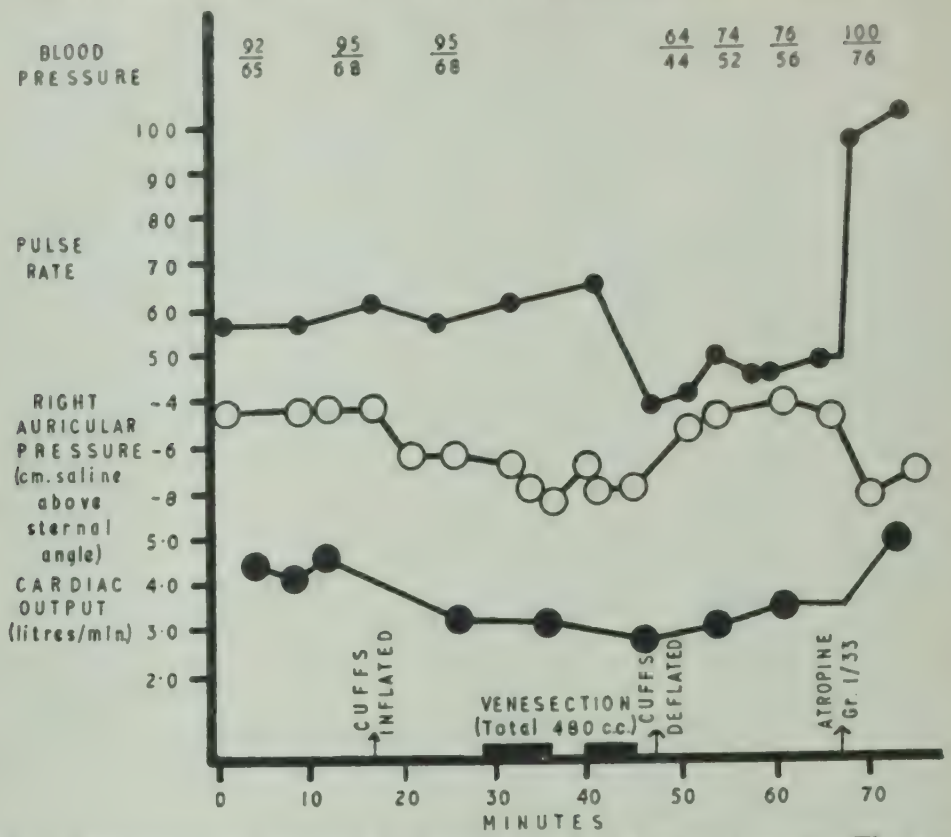

FIG. 4. A vasovagal faint produced by lowering the right auricular pressure. There was a fall in blood pressure and slowing of the pulse rate during venesection (Subject B 26).

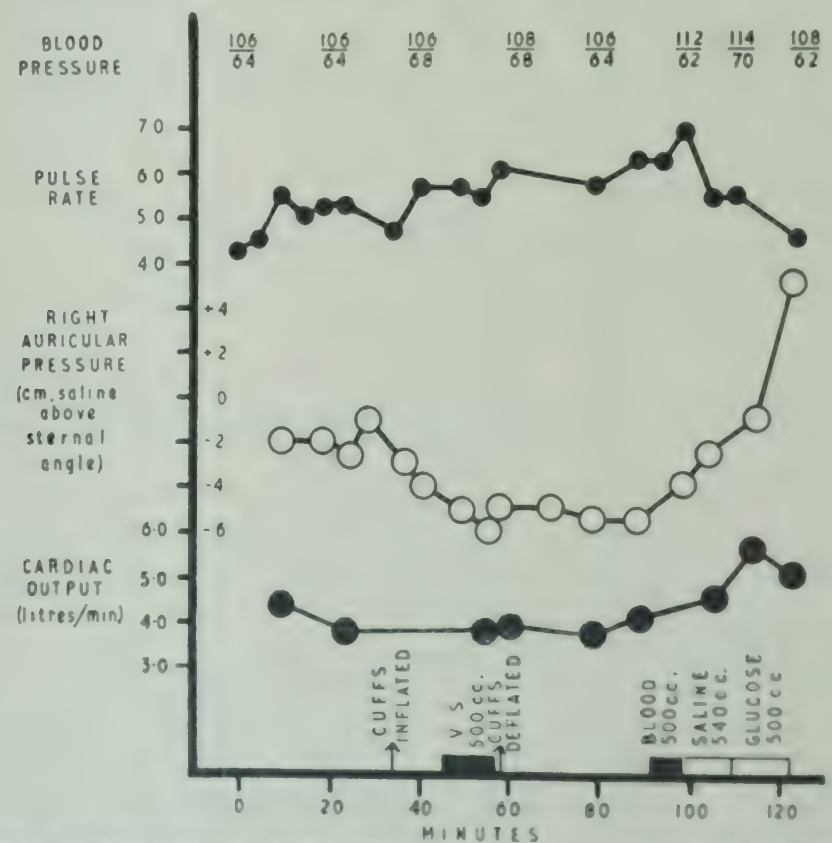

FIG. 5. In this subject (B 83) lowering the right auricular pressure by inflated cuffs on the thighs and venesection did not alter the cardiac output.

one was only 2·9 litres per min. Stroke volume was increased, often conspicuously so, in about half the subjects. Arteriovenous oxygen differences were generally slightly below normal, especially when the ages of the subjects were

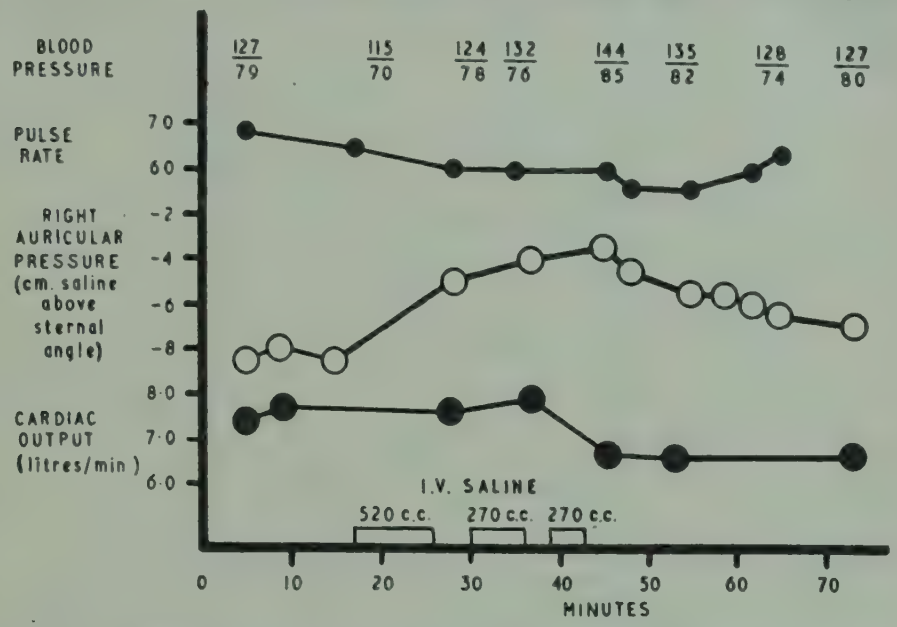

FIG. 6. The effect of raising the right auricular pressure by intravenous infusion on cardiac output, pulse rate and blood pressure (Subject B 75).

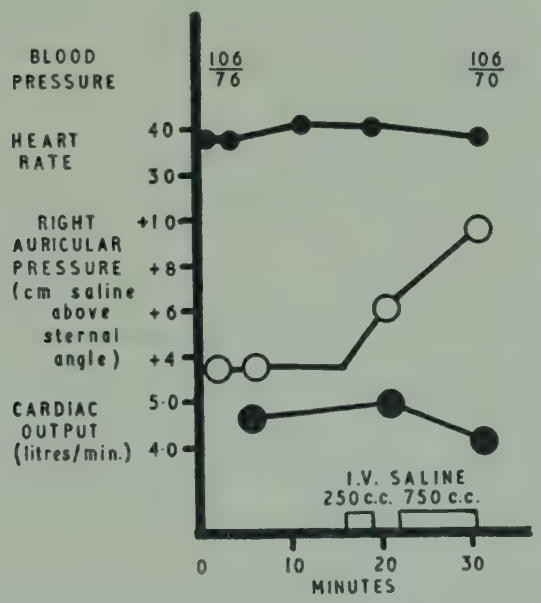

FIG. 7. The effect of raising the right auricular pressure by intravenous infusion on cardiac output, pulse rate and blood pressure (Subject B 36).

taken into consideration (Fig. 1). The oxygen saturation of the arterial blood was normal, but the oxygen consumption was usually below normal.

Response to changes in the venous filling pressure. The right auricular pressure was lowered in one subject by venesection alone, and in three subjects by venesection after cuffs had been applied to the thighs. The results are shown in Figs. 2, 3, 4, and 5. In the first three subjects, lowering the auricular pressure in

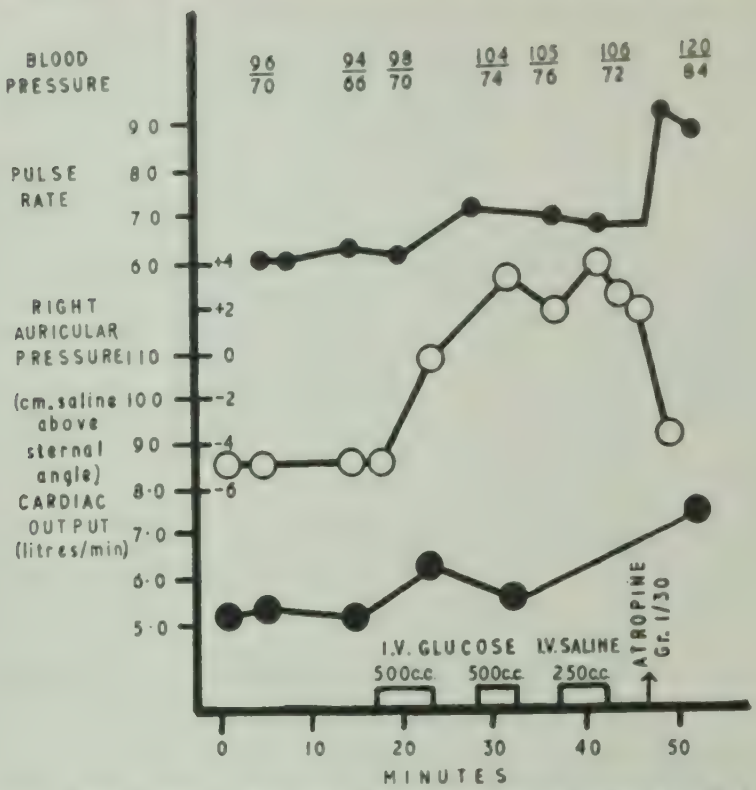

FIG. 8. The effect of raising the right auricular pressure and of atropine on cardiac output, pulse rate and blood pressure (Subject B 88).

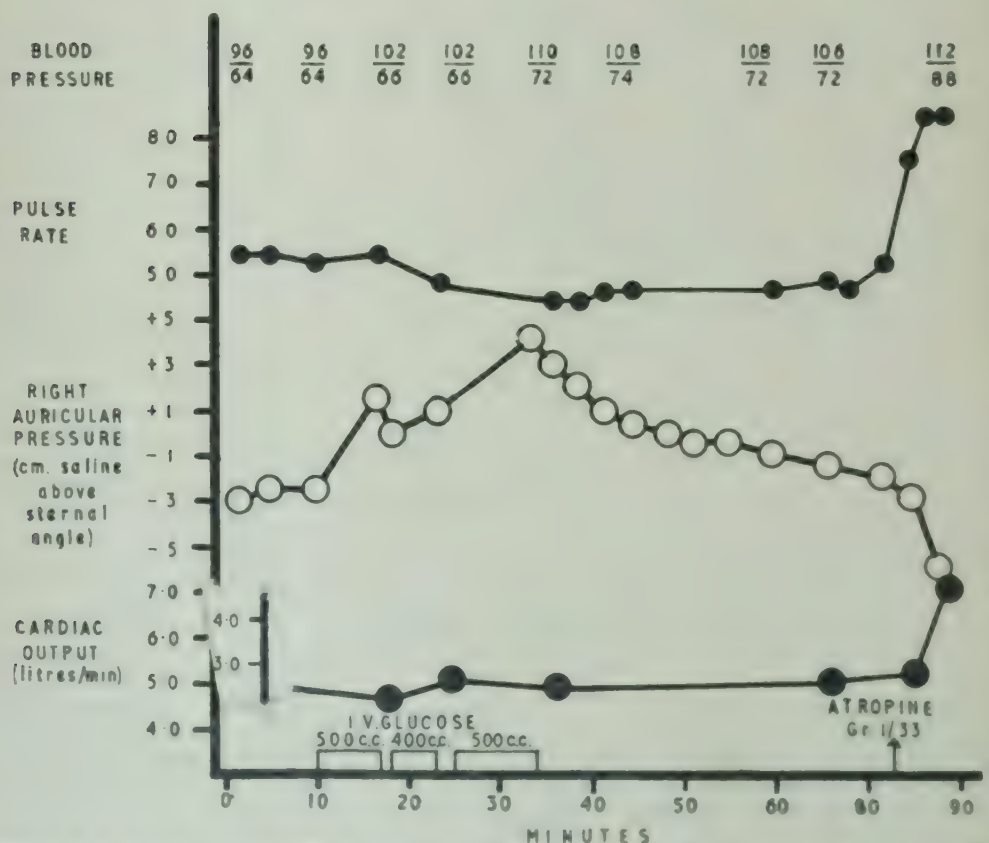

FIG. 9. In this subject (B 76) there was no change in cardiac output in response to an increase in right auricular pressure.

these ways reduced the cardiac output as it has been shown to do in the normal subject by McMichael and Sharpey-Schafer (1944a), but to a surprisingly small

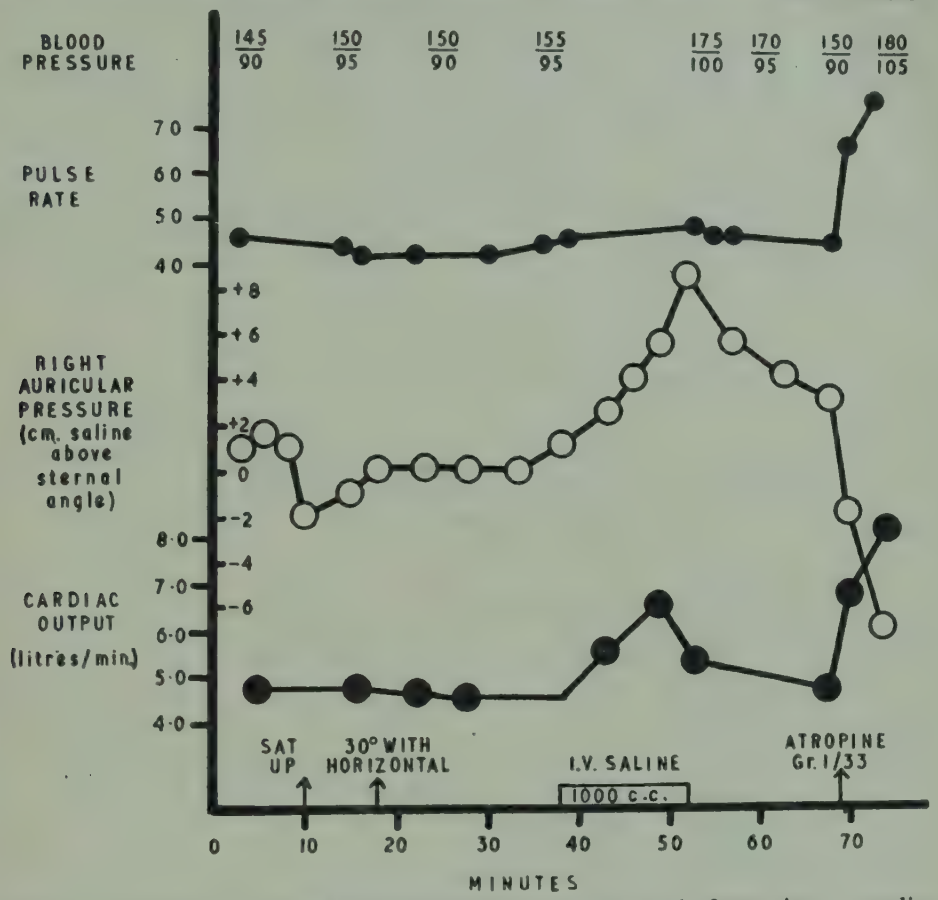

FIG. 10. The effect of raising the right auricular pressure and of atropine on cardiac output, pulse rate and blood pressure (Subject B 37).

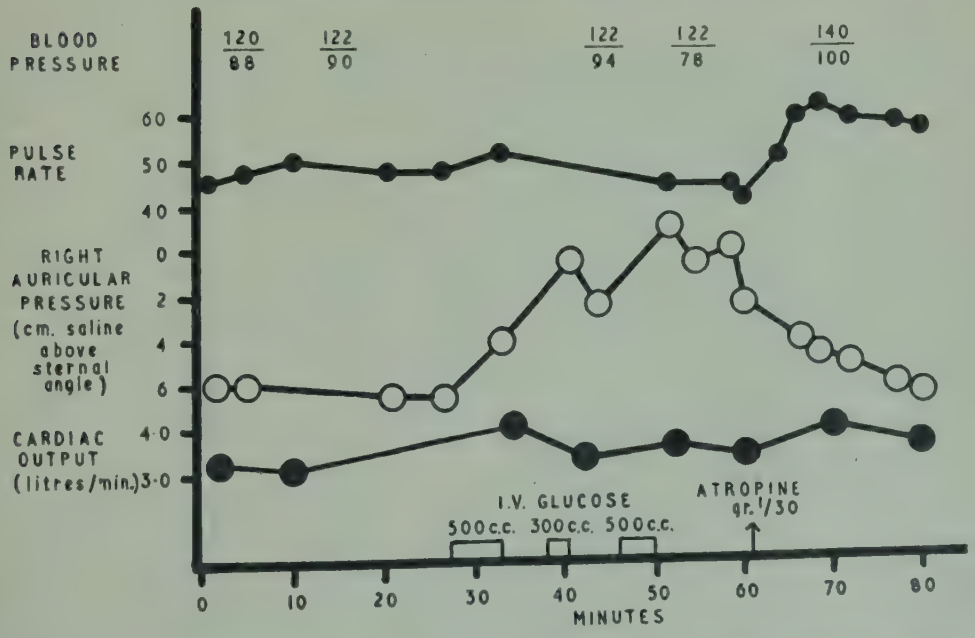

FIG. 11. The effect of raising the right auricular and of atropine on cardiac output, pulse rate and blood pressure (Subject B 85).

degree considering the magnitude of the pressure change. In the third subject (Fig. 4), the second venesection produced a vasovagal reaction, as indicated by a sudden fall in the pulse rate and in the arterial blood pressure, but little further change in cardiac output (Barcroft, Edholm, McMichael and Sharpey-Schafer, 1944). The fourth case showed no significant change in cardiac output (Fig. 5).

Right auricular pressure was raised in seven subjects by infusions of saline or glucose (Figs. 6–12). In six cases this was at first followed by a rise in cardiac output as in normal subjects (McMichael and Sharpey-Schafer, 1944a), but the increase was small, sometimes very small, considering the degree to which the pressure was raised. B76 (Fig. 9) did not show a rise in cardiac output in response

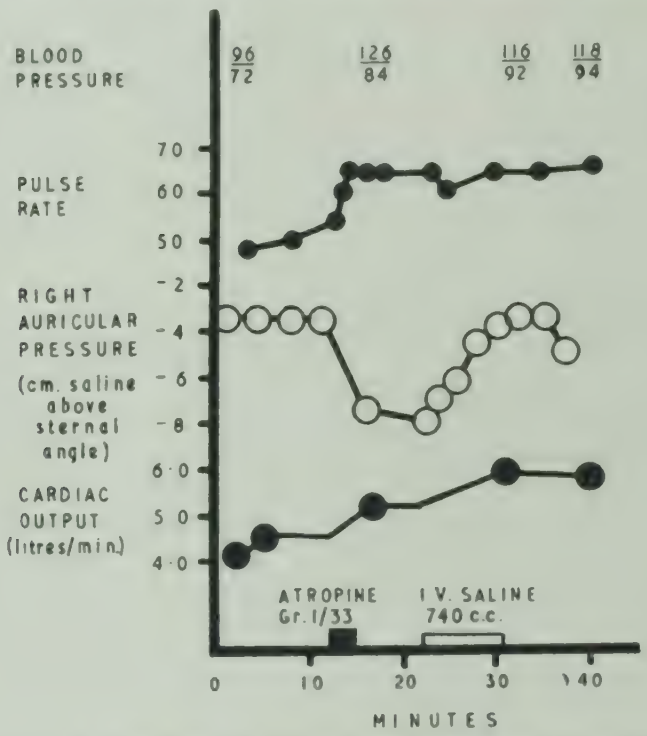

FIG. 12. The effect of raising the right auricular pressure and of atropine on cardiac output, pulse rate and blood pressure (Subject B 70).

TABLE 2

Effects of postural changes on the circulation of three subjects

Subject No.	Right auricular pressure (cm. saline above sternal angle)	Arterio-venous O_2 diff. (c.c./l.)	Cardiac output (l./min.)	Pulse (beats/min.)	Blood pressure (mm. Hg)	Angle of trunk with horizontal
B 37	+1·0	35·3	4·7	46	145/90	30°
	−1·0	35·2	4·7	42	150/95	80°
B 65	−2·5	38·3	5·2	50	128/90	30°
	−8·5	48·2	4·1	56	132/86	90°
B 91	−5·0	35·1	6·2	62	148/90	30°
	−3·5	50·1	4·4	70	160/106	90°
						Feet over bed edge

to considerable changes in auricular pressure. These infusions scarcely altered the heart rates, but the blood pressures tended to rise. In five subjects a further increase in venous filling pressure led to a fall in cardiac output, and a decrease in cardiac output was also recorded in B83 (Fig. 5) towards the end of his retransfusion after bleeding. In spite of a fall in cardiac output, the blood pressure rose above its previous level in three subjects. The total amount of intravenous fluid required to produce a fall in cardiac output was 800 to 1,000 c.c.

The effects of posture on the mean right auricular pressure and cardiac output are shown in Table 2. B65 and B91 showed the usual fall in cardiac

TABLE 3

Effects of atropine administered intravenously

Subject No.	Right auricular pressure (cm. saline above sternal angle)	Cardiac output (l./min.)	Pulse (beats/ min.)	Blood pressure (mm. Hg)	Remarks
B 10	−2·0	4·3	96	100/70	After digoxin 1·0 mg. i.v.
	−3·5	5·1	120	96/70	After atropine gr. 1/33
B 26	−4·5	3·4	46	78/56	20 min. after faint after bleeding
	−8·0	4·8	100	108/76	After atropine gr. 1/33
B 37	+3·0	4·7	44	150/90	After infusion 1,000 c.c. saline
	−6·0	8·1	76	180/105	After atropine gr. 1/33
B 64	−5·0	4·5	46	101/72	After venesection 440 c.c.
	−7·5	7·2	80	168/117	After atropine gr. 1/33
B 65	−5·5	4·9	46	128/70	After digoxin 1·5 mg. i.v.
	−7·0	8·3	72	152/90	After atropine gr. 1/33
B 70	−3·5	4·3	49	96/72	Initial readings
	−7·5	5·2	64	126/84	After atropine gr. 1/33
B 76	−2·0	5·0	48	102/70	After infusion 1,400 c.c. glucose
	−6·0	7·1	84	112/88	After atropine gr. 1/33
B 85	−2·5	3·4	42	122/78	After infusion 1,300 c.c. glucose
	−5·0	4·0	62	140/100	After atropine gr. 1/30
B 88	+3·0	5·5	68	105/76	After infusion 1,000 c.c. glucose and 250 c.c. saline
	−4·0	7·3	90	110/88	After atropine gr. 1/30
B 92	−3·0	6·0	48	126/70	After cuffs and venesection 350 c.c.
	−3·5	8·1	84	160/82	After atropine gr. 1/30

output on raising the trunk. There was no fall in B37 in spite of the reduction in auricular pressure.

Response to changes in heart rate. Schittenhelm and Schlecht (1918, 1919) found that atropine did not raise the pulse rate in undernourished subjects, and these observations have generally been accepted as correct (Bansi, 1946).

TABLE 4

Effects of exercise

Subject No.	Arteriovenous O_2 diff. (c.c./l.)	Blood pressure (mm. Hg)	Pulse (beats/min.)	Remarks
B 74	39·3	94/52	52	Before exercise
	45·8	96/54	72	After exercise
B 78	47·1	130/72	56	Before exercise
	65·0	142/75	68	After exercise
B 79	62·0	140/80	54	Before exercise
	80·0	168/92	112	After exercise
B 80	39·8	114/66	56	Before exercise
	55·0	120/72	62	After exercise
B 90	36·3	115/68	60	Before exercise
	45·4	118/65	60	After exercise

Moritz (1919), however, obtained a normal response to atropine. In the present series atropine always produced an increase in the heart rate, whether it was given before or after venesection or infusion (Table 3). The output of the heart increased, often to a considerable extent, as in normal subjects (McMichael

TABLE 5

Effects of intravenous digoxin

Subject No.	Time	Right auricular pressure (cm. saline above sternal angle)	Cardiac output (l./min.)	Arterio-venous O_2 diff. (c.c./l.)	Pulse (beats/min.)	Blood pressure (mm. Hg)	Dose
B 10	Before	−2·5	3·6	43·7	98	100/70	1·0 mg.
	After	−2·0	4·3	36·5	96	100/70	
B 65	Before	−4·5	4·6	43·8	52	134/89	1·5 mg.
	After	−5·5	4·9	40·8	45	128/70	
B 74	Before	±0	6·1	41·4	52	89/56	1·5 mg.
	After	−0·5	6·4	39·3	52	94/52	

and Sharpey-Schafer, 1944a), and this was true even in B76 in whom changes in the venous filling pressure produced no change in output (Fig. 9). McMichael and Sharpey-Schafer described a secondary fall in cardiac output after atropine injection and attributed it to a fall in the right auricular pressure, but in the present observations the output did not fall until the rate began to decrease.

Atropine was given to B70 (Fig. 12) before infusion to raise the pulse rate to a more normal level. This resulted in reduction of the right auricular pressure and augmentation of the cardiac output and blood pressure to normal levels.

Response to exercise. When the feet were exercised against resistance the arteriovenous oxygen difference increased as in normal subjects. The heart rate increased in all cases except one, and the blood pressure tended to rise (Table 4). Measurements of oxygen consumption during exercise were not made.

Response to intravenous digoxin. 1·0 or 1·5 mg. of digoxin were given to three subjects (Table 5). Changes in right auricular pressure were slight and in cardiac output insignificant. The changes reported by McMichael and Sharpey-Schafer (1944b) in normal subjects after intravenous digoxin were also of a small order.

TABLE 6

Effects of aneurin administered intravenously

Subject No.	Time	Right auricular pressure (cm. saline above sternal angle)	Arterio-venous O_2 diff. (c.c./l.)	Cardiac output (l./min.)	Pulse (beats/min.)	Blood pressure (mm. Hg)	Dose
B 79	Before	−4·5	62·5	2·9	52	140/80	20 mg.
	47 min. after	−5·0	60·2	3·0	55	112/70	
B 80	Before	−5·0	47·2	3·8	56	120/76	20 mg.
	36 min. after	−5·0	50·5	3·6	52	120/78	
B 90	Before	−6·0	41·4	6·2	60	112/70	40 mg.
	56 min. after	−5·5	41·5	6·2	54	112/68	
B 91	Before	−5·0	41·1	5·3	67	144/88	60 mg.
	40 min. after	−5·0	35·1	6·2	64	148/90	

Response to aneurin. Aneurin was given intravenously to four subjects in doses of 20 to 60 mg. (Table 6). These doses produced no significant circulatory changes within one hour, the maximum period of observation. Although B91 showed a slight increase in cardiac output, no improvement could be detected clinically on the following day.

Response to thyrotropic hormone. An active preparation (Organon, 200 Heyl-Laqueur units per c.c.) was given to two of the subjects in doses of 2 c.c. per day, and the results observed clinically. The thyroid became palpable in both cases. In the first case the heart rate rose from 52 to 78 and the blood pressure from 94/64 to 105/78 after two injections. In the other the pulse rate increased from 48 to 88, and the blood pressure from 94/— to 122/80 after five doses. After the fourth dose the basal metabolic rate of the second subject, which was originally −13 per cent, had risen to + 9 per cent. Cases of complete thyroid deficiency do not show any response to thyrotropic hormone (Sharpey-Schafer and Schrire, 1939).

TABLE 7

Bloodflow through the hand at rest in a waterbath at 34·0° C.

Subject No.	Blood pressure (mm. Hg)	Hand flow (c.c./100 c.c./min.)
B 36	100/80	1·3
B 37	108/72	1·2
B 70	103/73	2·4
B 76	100/68	1·8
B 79	110/72	3·0
B 83	132/84	1·7
B 85	94/–	2·0
B 88	108/–	3·0
B 92	118/80	0·9

Peripheral Circulation

The bloodflow through the hand was studied in nine subjects and the results are shown in Table 7. The resting bloodflow was considerably decreased below the normal average of 3·7 c.c. per 100 c.c. of hand per minute (Freeman, 1935).

TABLE 8

Bloodflow through the forearm at rest in a water bath at 34·0°C.

Subject No.	Blood pressure (mm. Hg)	Forearm flow (c.c./100 c.c./min.)
B 26	108/82	3·2
B 36	100/78	3·4
B 37 (A)	110/75	1·3
B 37 (B)	120/75	2·9
B 70	102/70	1·3
B 76	96/70	1·7
B 79*	130/86	2·1
B 83	130/78	2·3
B 85	94/–	1·2
B 88 (A)	102/80	1·5
B 88 (B)	90/66	1·0
B 92	110/72	1·1

* Developing gastric discomfort.

Twelve estimations of bloodflow through the forearm were made on 10 subjects (Table 8). Bloodflow was generally reduced. Only three estimations approached the normal average of 3·4 c.c. per 100 c.c. of forearm per minute (Barcroft and Edholm, 1946). One was in an apprehensive young subject, B26. Another subject, B37, whose resting bloodflow averaged 1·3 c.c. per 100 c.c. of forearm per minute on admission, showed a flow of 2·9 c.c. three days later when the systolic blood pressure had risen from 110 to 120 mm. Hg.

Vascular responses. Forearm bloodflow decreased when a rapid infusion of saline had raised the jugular venous pressure to 6 cm. above the level of the sternal angle (Fig. 13). Since a rise in arterial blood pressure accompanied the decreased flow, the forearm blood vessels must have constricted. This response to raising the auricular pressure to a high level has been observed in cachectic (Howarth, unpublished observations) and in normal subjects (Howarth and Sharpey-Schafer, 1947).

The two subjects in whom reactive hyperaemia was investigated responded normally to arterial occlusion for one minute. In one there was a transient volume increase on release and in the other a plateau before the usual shrinkage in volume took place (Lewis and Grant, 1925; Edholm and Howarth, unpublished observations). Flows recorded on release of the occlusion showed good dilatation to approximately normal values.

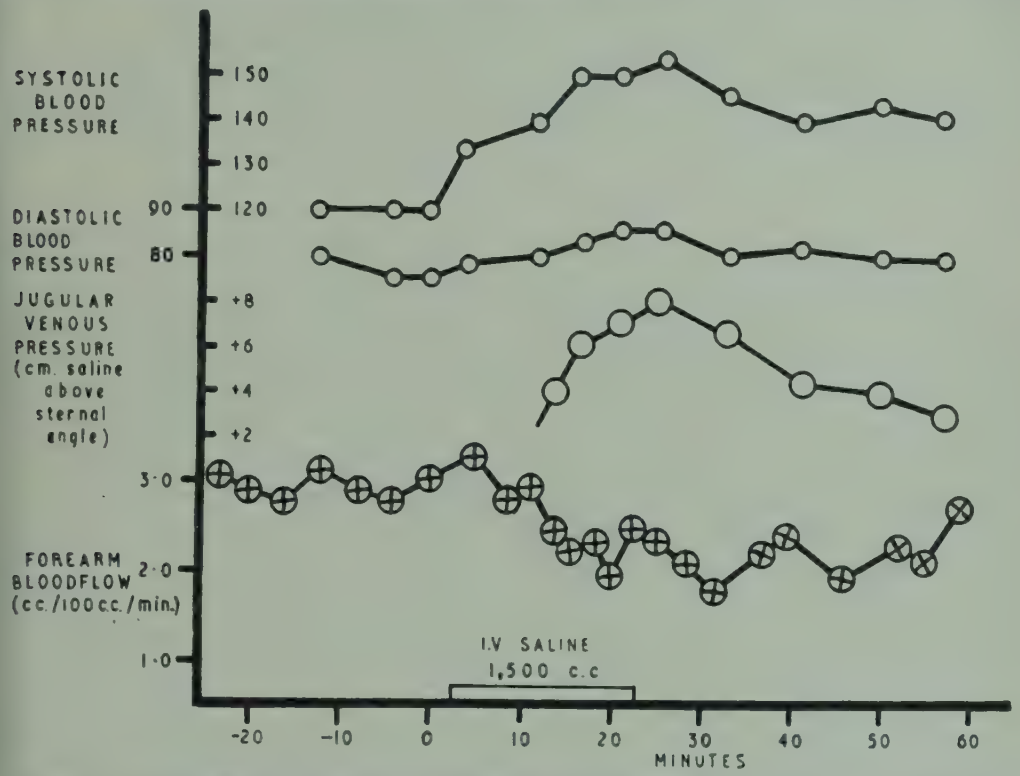

FIG. 13. An infusion of saline raised the venous pressure and caused a decrease in forearm flow and a rise in blood pressure. Constriction therefore occurred in forearm vessels (Subject B 37).

TABLE 9

Effects of heating the legs on the bloodflow through the forearm

Subject No.	Initial flow (c.c./100 c.c./min.)	Release begins		Max. flow (c.c./100 c.c./min.)	Total duration of heating (min.)	Blood pressure (mm. Hg)	
		Time (min.)	Flow (c.c./100 c.c./min.)			Initial	Final
Normal (Barcroft, Bonnar and Edholm, 1947)	3·1	15–35	—	9·3	—	—	—
B 37	1·3	12	2·2	6·1	49	110/75	120/80
B 70	1·3	23	2·3	2·5	45	102/70	103/67
B 83	2·3	22	3·2	4·8	42	130/78	124/74
B 85	1·2	35	1·6	2·3	41	94/–	98/–

Heating the legs affected the bloodflow through the forearm of four subjects as shown in Table 9, and the normal averages given by Barcroft, Bonnar and Edholm (1947) are included for comparative purposes. In all four subjects there was a release of vasoconstrictor tone. Only the first man showed the usual threefold increase in bloodflow, and in none did the maximum value reach the normal average level of 9·3 c.c. per 100 c.c. of forearm per minute. The changes in arterial blood pressure during the period of heating were insignificant.

After five daily doses of the thyrotropic extract (Organon) there was an increase in forearm bloodflow from 1·2 to 2·1 c.c. per 100 c.c. per minute. The rise in blood pressure of this subject (from 94/— to 122/80) is referred to above.

DISCUSSION

The majority of these undernourished subjects had a subnormal oxygen consumption, but since the arteriovenous oxygen difference was seldom increased and was often reduced below the normal value, the calculated cardiac output was usually within the normal range. When the oxygen consumption of the body is reduced to comparable levels by thyroid deficiency, the arteriovenous oxygen difference is generally greater than normal (Howarth and Sharpey-Schafer, to be published), and hence the output of the heart is low. In cases of severe anaemia (Sharpey-Schafer, 1944) and early cor pulmonale (Richards, 1945; Howarth, McMichael and Sharpey-Schafer, 1947) in which arteriovenous oxygen differences are also less than normal, the oxygen consumption is generally slightly increased and the calculated cardiac output is therefore raised above normal values (Fig. 14). Increased oxygen consumption and decreased arteriovenous oxygen differences are also found in thyrotoxicosis (Howarth and Sharpey-Schafer, to be published). Landes (1943) attempted to explain his relatively normal arteriovenous oxygen differences on the grounds that oedema of the tissues interfered with the peripheral utilization of oxygen. Harrison and Pilcher (1930) showed that the arteriovenous oxygen difference was reduced in an oedematous limb, though Weiss and Ellis (1935) were unable to confirm this, and the explanation will not cover the present findings, since some of the subjects had no pitting oedema and others only a very little. It is possible that an excess of extracellular fluid (*McCance*, p. 21) may have reduced the utilization of oxygen in the peripheral tissues, but the normal increase in the arteriovenous differences on exercise makes any gross abnormality seem unlikely.

McMichael and Sharpey-Schafer (1944a) showed that the normal human heart responded to changes of filling pressure according to Starling's Law. This work has on the whole been confirmed in normal people (Howarth, McMichael and Sharpey-Schafer, unpublished observations), although occasionally young subjects have not shown any response. Warren, Brannon, Stead and Merrill (1945) and Warren, Brannon, Weens and Stead (1948) were unable to obtain the response in healthy young men. The Wuppertal subjects showed little or no change in cardiac output in response to considerable variations in venous filling pressure. The right auricular pressure appeared to be raised by the administration of 800 to 1,000 c.c. of fluid to a greater extent than is usual in the normal subject. It is also unusual in the normal heart to produce a secondary fall in cardiac output if the infusion is continued and the filling pressure raised still further. Patients with thyroid deficiency, however, have responded in this manner (Howarth and Sharpey-Schafer, to be published).

The mechanism of the rapid rise in venous pressure remains unexplained, but the fact that it occurs suggests that the greatest care should be exercised if undernourished people are to be given transfusions of blood or plasma, or if they are to receive any intravenous therapy. Lamy, Lamotte and Lamotte-Barillon

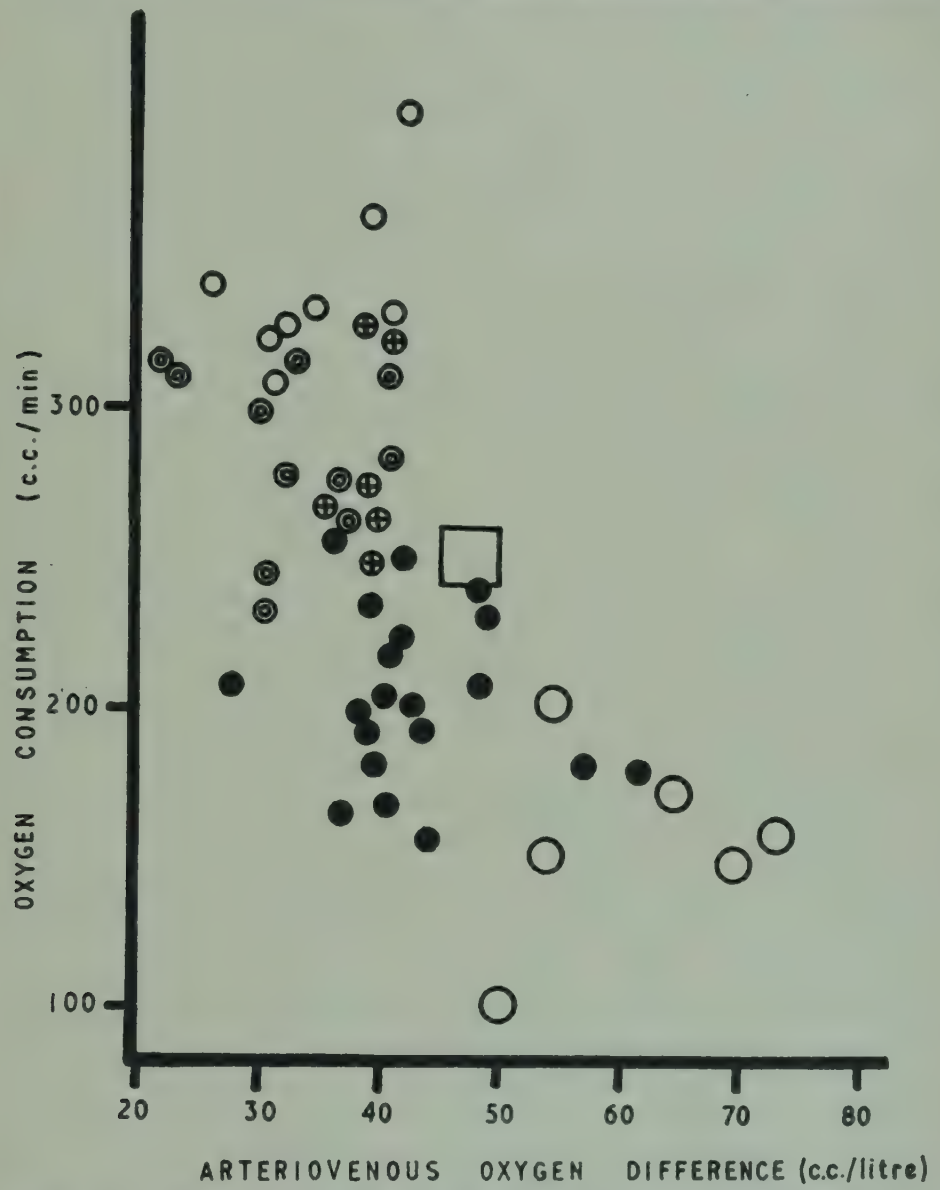

FIG. 14. Diagram comparing the relationship of oxygen consumption to arteriovenous oxygen difference in undernourished subjects (black dots) with that in patients with thyroid deficiency (large clear circles) in whom oxygen consumption is also subnormal, and in patients with thyrotoxicosis (small clear circles), severe anaemia (double circles) and early cor pulmonale (circles with crosses), in whom arteriovenous oxygen difference is below normal. The large square represents values obtained in normal subjects. None of the results were obtained under strictly basal conditions.

(1946) described a "flooding syndrome" in undernourished prisoners in German concentration camps: two dehydrated and five oedematous patients died rapidly with pulmonary oedema following plasma transfusions. Nevertheless, Lamy *et al.* considered that blood and plasma were of benefit, but their own experiences and the evidence presented here suggests that intravenous fluids should always be given with caution.

Right auricular pressure was above normal in half the present subjects. Bansi (1946) noted a transient enlargement of the liver in patients with hunger oedema, but he did not record the venous pressure. Previous investigators (Govaerts and Lequime, 1942; Cardozo and Eggink, 1946; Keys *et al.*, 1946) found that the peripheral venous pressure was reduced by undernutrition, but this may perhaps have been the result of a low peripheral bloodflow and not an indication of pressure in the right auricle. The cause of the raised venous pressure is at present uncertain. There was no radiological or electrocardiographic evidence of pericardial effusion. The responses to variation in venous filling pressure were not the same as those observed in cases of low output heart failure due to ischaemic, valvular or hypertensive heart disease (Howarth, McMichael and Sharpey-Schafer, 1946). A raised venous pressure associated with oedema and an increased blood volume was found in patients to whom an overdose of desoxycorticosterone acetate had been given (Ferrebee, Ragan, Atchley and Loeb, 1939) and in normal subjects following the administration of large quantities of sodium salts (Lyons, Jacobson and Avery, 1944; Grant and Reischsman, 1946), but detailed circulatory studies were not made.

Low blood pressure may result from a diminished cardiac output or a decreased peripheral resistance. In some of the present subjects the reduction of cardiac output was sufficient to account for the low blood pressure and the total peripheral resistance was within normal limits (Table 1). In others, since the cardiac output was relatively normal, there must have been a lowered peripheral resistance to account for the low blood pressure. The bloodflow through the skin and muscles, however, was diminished, and the renal bloodflow was relatively normal in the patients in whom it was investigated (*McCance*, p. 175). There may have been vasodilatation in the splanchnic area. There is little evidence to support the view of Landes and Arnold (1947) that the presence of oedema increased the total peripheral resistance of the body.

Bloodflow was rather more reduced in the hand than in the forearm. In B83 and B36, for instance, the hand flows were below normal although the forearm flows were within the limits of normality. Peripheral bloodflow depends on the arterial pressure and on the state of tone of the vessels. It is possible that the reduced forearm flows resulted almost entirely from a decreased blood pressure, but that vasoconstriction was present in the hand where the flow was more conspicuously reduced. The blood supply to the skin of the hand was, however, sufficient to prevent trophic changes and cyanosis. The reduction in total hand flow might possibly be due to a reduction in blood flowing through the arteriovenous shunts, resulting in the conservation of heat in subjects with a considerably reduced basal metabolic rate. The present results in undernourished subjects differ from those of Scott and Morton (1931), who found very high resting skin temperatures in the toes and the soles of the feet in three cases of cachexia due to advanced carcinoma. Reduction in peripheral bloodflow would not seem to result from oedema. None of the limbs under observation showed pitting oedema, though latent oedema may have been present. It has been shown, moreover, by Abramson, Fierst and Flachs (1943) that bloodflow is actually increased in oedematous limbs.

The response of forearm vessels to ischaemia produced by arterial occlusion appeared to be normal. The response to local temperature changes was not studied, but there was evidence that the vasomotor nerves were intact and the vessels responsive. A rapid rise of auricular pressure to high levels led to constriction of the vessels in the forearm, which is believed to be a nervous reflex

(McDowall, 1934; Howarth and Sharpey-Schafer, 1947). Lowering the right auricular pressure in one subject resulted in a vasovagal faint, with the characteristic acute fall in blood pressure due to muscle vasodilatation, a reflex whose efferent pathway is by the vasomotor nerves (Barcroft and Edholm, 1945). Release of vasoconstrictor tone by indirect heating (Grant and Holling, 1938) produced an increase in bloodflow, which however did not reach normal levels in three of the four subjects studied, and seemed too small to be the result of a low blood pressure alone. In persons with thyroid deficiency, whose resting bloodflow through the forearm is very low, heating results in a rise in the bloodflow to normal levels and a fall in blood pressure (Howarth and Sharpey-Schafer, to be published).

It is, however, impossible to say that some degree of thyroid or pituitary deficiency did not contribute to the circulatory state. This study shows that the circulatory changes were not characteristic of a pure deficiency of either vitamins or hormones. The combination of a slow pulse, a low pulse pressure, a small heart, and a normal cardiac output and peripheral constriction would seem to exclude a deficiency of aneurin (Wenckebach, 1934). It has already been pointed out that, although the reduction in oxygen consumption resembled that found in myxoedema, the cardiac output and the peripheral bloodflow findings differed in several respects.

Study of the circulation has thrown little light on the aetiology of hunger oedema. Right auricular pressure was raised in half the subjects, but in no case to very high levels, and raised venous pressure alone is unlikely to be responsible for oedema formation (Smirk, 1936). Other mechanisms must be involved.

SUMMARY

1. The techniques of cardiac catheterization and venous occlusion plethysmography have been applied to the study of the circulation in a selected group of twenty Germans, all of whom suffered or had suffered from hunger oedema.

2. The pulse rates were slow and the arterial blood pressures were below expected levels in many cases. The jugular venous pressure was often raised. The extremities were not cold and blue.

3. Resting cardiac output was variable, but most commonly slightly subnormal. Right auricular pressure was raised in half the cases. Oxygen consumption was usually below normal, while the oxygen saturation of the arterial blood was normal.

4. Reducing the right auricular pressure by venesection and by applying sphygmomanometer cuffs to the thighs resulted in a very small fall in cardiac output. Intravenous infusions produced, first, a rise in output which was very small considering the magnitude of the changes in the filling pressure, then a secondary fall in cardiac output if the infusion was continued. The rise in auricular pressure produced by 800 to 1,000 c.c. of intravenous fluid appeared to be greater than in normal subjects. The administration of intravenous infusions to undernourished persons may, therefore, prove dangerous.

5. The response of cardiac output to an increased heart rate produced by atropine was normal. Further reduction of the already slow heart rate occurred during a vasovagal faint.

6. The arteriovenous oxygen differences, which were generally normal or slightly diminished, increased on exercise.

7. Intravenous digoxin had little effect on the venous pressure, and the changes in cardiac output induced by it were slight.

8. Aneurin (20–60 mg.) given intravenously to four subjects produced no significant circulatory response.

9. Resting bloodflow through the hand was low. Forearm bloodflow was also reduced, but not to so great an extent.

10. The forearm vessels constricted when right auricular pressure was raised to high levels. There was a normal response to the ischaemia produced by arterial occlusion. Release of vasoconstrictor tone occurred when the feet were heated.

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XXI. RADIOLOGICAL OBSERVATIONS ON THE SIZE OF THE HEART

by F. R. BERRIDGE

BOTH the cardiac musculature and the blood contained in the heart produce shadows on the fluorescent screen or X-ray film, so that a change in the dimensions of the shadow may be due to an alteration in either or both of these components. Both of them have to be considered in explaining why the heart may appear to have changed in size. Unfortunately, the only method of study which allows one to differentiate the blood in the chambers from the musculature of their walls is angiocardiography, and the severity and possible dangers of this procedure preclude its use as a routine test. An indirect approach to the problem has, therefore, been made by considering the literature dealing with the fate of the cardiac muscle in animals which have been starved, and in undernourished human beings.

PREVIOUS OBSERVATIONS

Animal Experiments and Post-mortem Findings

In 1843, Chossat carried out experiments on pigeons. He found that during complete starvation they showed a loss in heart weight of 44·8 per cent for a loss of 42·3 per cent in the weight of the voluntary muscles. Voit (1866) starved one cat for 13 days and killed it, using another cat as a control. He concluded that this treatment reduced the weight of the heart by 2·6 per cent of its initial weight, but that of the skeletal musculature by as much as 30·5 per cent. As Keys, Henschel and Taylor (1947) have pointed out, this unfortunate experiment has been handed down from textbook to textbook. Sedlmair (1899) carried out some further experiments on cats. He sacrificed one as a control and starved two others for 28 and 35 days respectively. The percentage loss of weight (in the fresh state) of the hearts of these two cats worked out at 29 and 38 per cent. Schieffer (1907) made orthodiagrams of dogs' hearts before and after periods of undernutrition varying from nine days to two months. The cardiac areas diminished by 8 to 23 per cent, and then after a period of normal nutrition slightly exceeded their initial size. Two dogs of the same weight were obtained; one was killed after being given a normal diet for four weeks and the other after four weeks' starvation. The heart of the starved dog weighed 32 per cent less than that of the control. Heitz (1912) observed that in Schieffer's orthodiagrams the width of the vascular shadow was smaller during the starvation period. He also found that rabbits' hearts lost 23·5 per cent of their initial weight when their bodies had been reduced by total starvation by 36 per cent. On partial starvation he found a loss of 7·46 per cent for the heart and 10·5 per cent for the body weight. When guinea-pigs were starved till their bodies had lost 34 per cent of their original weights, their hearts were found to have lost 20·3 per cent of their weight. Microscopically, most of the fibres were normal in structure. A few fibres were fragmented and others were atrophied. The dimensions of the fibres diminished from 13·1 × 10·5 μ to 11·1 × 7·3 μ, and there was a similar decrease in the size of the nuclei.

Morgulis (1923) summarized the literature on animal experiments and quoted the reports of some Russian observations to which access is at present difficult. He stated that Lasarev (1895), who conducted detailed experiments on

guinea-pigs, found that all organs did not lose weight at the same rate during starvation; the heart lost a smaller percentage of its weight than did the body as a whole until emaciation was extreme. In McCarrison's (1921) experiments on pigeons, guinea-pigs and monkeys, the hearts of the underfed animals were found to be considerably lighter than those of the controls. Only in monkeys fed on "autoclaved food, butter and onions" did any of the weights of the hearts fall inside the normal range. McCarrison's experiments were designed to cause vitamin deficiency, and did not therefore give rise to uncomplicated Calorie deficiencies. Jackson (1915) found that the hearts of albino rats normally accounted for 0·43 per cent of the body weight and that this percentage was not changed by complete or incomplete starvation.

Thus animal experiments have made it clear that the weight of the heart decreases during a period of undernutrition. In rabbits and guinea-pigs the hearts have tended to lose a smaller percentage of their initial weight than the whole body, but in pigeons and albino rats the losses have been about the same.

The post-mortem examination of the heart in man supports the results of the animal experiments. Boyd's (1861) tables show a correlation between the weight of the heart and that of the body in paupers who had died in varying stages of undernutrition. Müller (1883) carried out an extensive investigation of the weight of the heart and examined 1,481 dead bodies for this purpose. He showed that the ratio between the weight of the heart and that of the body steadily declined as the weight of the body increased. Bell and Hartzell (1924) examined 2,071 cadavers, and found that there was no increase in heart weight with age unless there was a coincident increase in body weight. Smith (1928) confirmed this, and found that the heart weighed 0·43 per cent of the total body weight in males, and 0·40 per cent of the body weight in females. The figures were slightly higher in thin and lower in obese persons, which agreed with the findings of Müller (1883). Bean and Baker (1919) performed 1,534 autopsies and found that the absolute weight of the heart increased with the stature, age and nourishment of the subject. Nourishment exerted the greatest effect, and stature the least. On the basis of 571 necropsies in children, Bovaird and Nicoll (1906) found that the heart weight was directly proportional to the height and the state of nutrition of the child.

There are many reports in the literature of the first world war on the post-mortem appearances of the heart in people suffering from hunger oedema. Cardiac atrophy was observed by nearly all investigators, but Gerhartz (1917) found neither cardiac dilatation nor any alteration in the cardiac musculature. Brown atrophy of the heart muscle was reported by Rumpel and Knack (1916), Hülse (1917), Paltauf (1917), Schittenhelm and Schlecht (1918), Lewy (1919) and von Hoesslin (1919). According to Park (1918) the cardiac muscle was pale and flabby and there was moderate dilatation of the ventricles. Lewy (1919) described the heart muscle as limp, and he frequently found the right side of the heart dilated. Where the weight of the heart has been mentioned, it has always been reported to be diminished. According to Hülse (1917), the weight of the heart was sometimes as low as 145 g. Oberndorfer (1918), who accepted the normal weight of the heart as being 250 g. to 320 g., observed that the weight of the heart in undernourished persons hardly ever reached 250 g., and sank as low as 150 g. Von Hoesslin (1919) reported that the weight of the heart varied from 210 g. to 260 g. and averaged 234 g. Paltauf (1917) stated that the portion of the great vessels lying within the pericardial sac was increased in relation to

the size of the heart, and that the combined weight of the heart and the great vessels inside the pericardium was nearly always under 300 g., and was only 200 g. in one man. The trabeculae were thinned, especially towards the apex, where they consisted of little more than endocardium. Menzies (1920), who made post-mortem studies of persons with hunger oedema dying in English Poor Law and insane institutions, found the auriculoventricular junction oedematous in nearly every case.

Burger, Sandstead and Drummond (1945), in their survey of Western Holland just after the second world war, found cardiac atrophy in some cases. In the Dachau concentration camp Rosencher (1946) reported that the hearts of the victims were small and flabby. Simonart (1945) reported that in five out of seven fatal cases of hunger oedema in the Louvain prison the heart muscle was oedematous and less firm than the normal. Uehlinger (Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948) investigated undernourished persons who had reached Switzerland from concentration camps. He found that in persons under 50 years old the weight of the heart varied from 160 g. to 220 g. but nearly always exceeded 200 g. In persons free from oedema in this age group the ratio of the weight of the heart to the weight of the body had maintained the normal value of 1 to 200. In persons over 50 the hearts weighed from 190 g. to 320 g., but again nearly always exceeded 200 g., in spite of a loss in body weight of 23 to 25 kg. The ratio between the weight of the heart and the weight of the body was almost invariably greater than 1 to 200. He considered that the hearts of the older subjects were to some extent protected from the effects of undernutrition. In only one case was gross enlargement of the heart found, and this was associated with brown atrophy of the musculature.

Clinical and Radiological Observations

Massive enlargement of the left ventricle was found, presumably by clinical methods, by Maase and Zondek (1917) in patients with nutritional oedema, which had recently been described as a clinical entity. Their subjects had slow pulse rates. Hülse (1917) reported that the absolute heart dullness was increased laterally in some patients with hunger oedema, but he attributed this to retraction of the margins of the lungs and not to cardiac enlargement. Schittenhelm and Schlecht (1918) investigated 200 persons suffering from oedema associated with a slow pulse rate. Clinically the heart was normal in size in the great majority of the subjects. Gross enlargement was found in two, the enlargement being to the right in one case and to the left in the other. No abnormality in the size or the shape of the heart was seen on the X-ray screen. The same authors (1919) reported that there was no radiological evidence of cardiac enlargement, but rather that the heart was abnormally small. Lewy (1919), investigating hunger oedema in prison camps, found by clinical methods that the heart was neither wider nor narrower than the normal.

Reports on the heart in the undernutrition resulting from the recent war have not been consistent. According to Burger *et al.* (1945) the hearts were normal at clinical examination. Dumont (1945), in Belgium, made orthodiagrams of the hearts of uncomplicated cases of hunger oedema and noted that in 15 patients the hearts were normal, in 6 the left side of the heart was a little enlarged, and in 5 there was slight generalized enlargement. No heart was smaller than the normal. Out of 17 other cases with oedema, 11 hearts were enlarged, one was normal in size, and 5 showed left ventricular enlargement associated with ascites. Dumont does not state on what criteria he diagnosed cardiac enlargement.

Rosencher (1946) reported that on the X-ray screen the heart beats of subjects in the Dachau concentration camp were of poor amplitude and the cardiac shadows were enormous. In his subjects the slow pulse rates were interrupted at times by prolonged periods of tachycardia. Just after the liberation of this camp Piatt (1946) took radiographs of the chests of 2,267 inmates and, using the cardiothoracic index as the criterion of enlargement, considered that 11·8 per cent of the hearts were enlarged. He suggested that the cardiac enlargement might be due to beriberi, but no clinical support for this view was forthcoming. Landes and Arnold (1947) found the heart measurements at the upper limits of the normal on the films taken at a distance of two metres and attributed this to the large stroke volumes. In experimental semi-starvation in man, Keys *et al.* (1947) found a decrease in the systolic volume of the heart and a diminished stroke volume measured radiologically. They used a formula for the calculation of the cardiac volume which took into account only the area of the frontal cardiac silhouette, but Liljestrand, Lysholm, Nylin and Zachrisson (1939) have shown that, if the volume of a heart is calculated from a formula which employs three dimensions of the heart, the figure obtained may differ by as much as 45 per cent from the volume calculated from a formula using only two dimensions. Keys *et al.* found that the mean cardiac volume of their subjects after 20 weeks on an improved diet, in the last eight weeks of which unlimited food was allowed, exceeded the mean initial volume by 2·3 per cent. In his studies of hunger oedema in Louvain prison, Simonart (1945) found that in some subjects the cardiac shadows were enlarged at radiological examination, and that in one person the measurements were unchanged after ten daily intravenous injections of 50 mg. of aneurin, but diminished after daily intravenous injections of 100 mg. aneurin had been given for eight days.

There is no doubt from the foregoing that the musculature of the human heart has been found to be decreased in weight by undernutrition if this has been severe enough to have caused oedema. The reports of the size of the living heart have, however, been conflicting.

PRESENT INVESTIGATION

Subjects

The hearts of 50 undernourished persons, 47 men and 3 women, who had attended the special out-patient department at the Städtisches Krankenhaus, Barmen, were examined by fluoroscopy, and their transverse diameters and frontal areas were measured radiologically. The subjects were aged from 20 to 80 years and averaged 51. Two weights have been recognized for each subject: first, his "actual" weight at the time of the examination, and second, his "previous" weight, i.e. the amount stated by the subject to have been his weight before he became undernourished. The subjects' losses of weight varied from 2 to 53 per cent and averaged 26 per cent of their previous weights. The pulse rates ranged from 39 to 84 beats per minute and averaged 59 beats per minute. Nineteen of these men were given an unlimited diet for eight weeks (*Widdowson*, p. 313), and their cardiac volumes, as well as the transverse diameters and frontal areas of their hearts, were measured both before and after the period of refeeding. In addition to these 50 subjects, a further 26 undernourished persons were examined by fluoroscopy only.

Radiological Technique

Postero-anterior films at a focus-film distance of two metres were taken of the 50 persons in the erect position, the exposures being made in inspiration.

Left lateral films at the same focus-film distance were also made of the 19 men who were given an unlimited diet for eight weeks. All the subjects were examined in the fasting state, having rested for at least 45 minutes before the examination. The transverse diameter of the cardiac silhouette was measured (in cm.) on each postero-anterior film. From each film the frontal cardiac area was calculated from the formula of Ungerleider and Gubner (1942):

$$A = \tfrac{\pi}{4} (L \times B)$$

where A is the area (in sq. cm.) and L and B are the long and broad diameters (in cm.) measured on the film. The cardiac volume was calculated from the Kahlstorf (1932) formula:

$$V = 0{\cdot}63 (A_c \times T.D._{hor})$$

V being the volume (in c.c.), A_c the area calculated by the formula given above, corrected for divergent distortion, and $T.D._{hor}$ the greatest horizontal antero-posterior diameter of the heart shadow on the lateral film, corrected for divergent distortion.

The theoretical transverse diameter and frontal cardiac area were predicted from the height and weight of each subject from the tables of Ungerleider and Gubner (1942), which were based on studies of 1,460 normal persons. These tables are applicable to adults of any age and either sex. The figures in these tables had the advantage that, since they had not been corrected for divergent distortion, they were directly comparable with the actual measurements made on each film. This eliminated the necessity for correcting all the transverse diameters and frontal areas. The values of the cardiac volumes were, however, corrected for divergent distortion, since cardiac volumes are usually expressed in this way.

Results

Seventy-six undernourished persons were examined fluoroscopically, and the results may be summarized as follows:

Sixty hearts were judged to be within the normal limits of size. Of these hearts, 29 showed abnormally large ventricular pulsation in the left anterior oblique position, but in only eight could it be seen in the frontal position.

Five hearts were on the large side of the normal, and in one of them the amplitude of the pulsations was increased.

Two hearts were generally enlarged with dimensions outside the normal range.

Nine hearts showed abnormal left ventricular enlargement, and three of these showed increased pulsation.

The subjects with the slowest pulse rates generally had the greatest pulsations. Two of these cases, however, with 39 and 48 beats per minute, did not show large pulsations; one of them had an enlarged left ventricle and the other had a heart of normal size.

Transverse diameter. From Table 1 it will be seen that the mean measured transverse diameter did not differ from that predicted from the heights and previous weights. It was, however, considerably larger than that predicted from the actual weights, and this difference is statistically significant ($t = 10{\cdot}4$, $P < 0{\cdot}01$). The histograms A and B in Fig. 1a show the frequency distributions of the differences between the measured transverse diameter and the transverse diameters predicted, firstly from the height and actual weight, and secondly from the height and previous weight. It will be seen that, whereas in the first case the majority of the differences lies on the positive side of the zero line,

TABLE 1

Transverse diameter and area of frontal heart silhouette
(Average of 50 observations)

Dimension	Radiographic measurement	Prediction from height and "actual" weight	Prediction from height and "previous" weight
Mean transverse diameter (cm.)	13·7	11·7	13·7
Standard deviation (cm.)	1·4	0·7	1·0
Mean area (sq. cm.)	129	115	123
Standard deviation (sq. cm.)	23	21	9

in the second case the differences are fairly evenly distributed on both sides of the zero line. Thus the observed transverse diameter corresponded more closely to the diameter to be expected from the person's previous weight than to that indicated by his present weight, and the loss of weight had not been followed by any change in the transverse diameter of the heart.

If the eight enlarged hearts are excluded, the difference between the mean measured transverse diameter and that predicted from the previous weights is still only 0·3 cm., which is well within the limits of experimental error. The mean figures are not affected when the observations on the three females are omitted. When the subjects were grouped according to their pulse rates, the means of the transverse diameters in the different groups did not differ significantly from those of the whole series. On correlating the transverse diameters with the loss of weight, it was found that only in the five subjects who had lost more than 40 per cent of their weight did the mean of the measured transverse diameters (12·4 cm.) differ greatly from the mean of the transverse diameters predicted from the previous weights (15·2 cm.). The measured value was nearer the mean of the transverse diameters predicted from the actual weights of these five subjects (11·2 cm.).

Area of the frontal silhouette. From Table 1 it will be seen that the mean area of the frontal silhouette calculated from the observed measurements exceeded that predicted from the heights and previous weights by 6 sq. cm. ($t = 2{\cdot}2$, $P = 0{\cdot}05$). It was considerably larger than that predicted from the actual weights, and the difference is statistically significant ($t = 5{\cdot}4$, $P = <0{\cdot}01$). The histograms C and D in Fig. 1b show the frequency distributions of the differences between the area calculated from the observed measurements and, firstly, the area predicted from the actual weight, and, secondly, the area predicted from the previous weight. Again, it will be seen that in the first case the majority of the differences lie on the positive side of the zero line while in the second case they are more evenly distributed on both sides of the zero line. Thus, as was found for the transverse diameters, the mean area of the frontal silhouette had not decreased in parallel with the loss of body weight. In the 5 subjects who had lost 40 per cent or more of their previous weights, however, the mean frontal area (113 sq. cm.) was almost identical with the mean area predicted from their actual weights (111 sq. cm.), whilst the mean area predicted from their previous weights was considerably higher (128 sq. cm.). In those subjects who had lost less than 40 per cent of their previous weights, however, the mean frontal area

exceeded the mean area predicted from the previous weights. Thus the areas were relatively smaller if the subject had lost much weight. It was found that the mean frontal area of those subjects with pulse rates under 50 beats per minute and of those with rates of 50 to 59 beats per minute (130 sq. cm. and

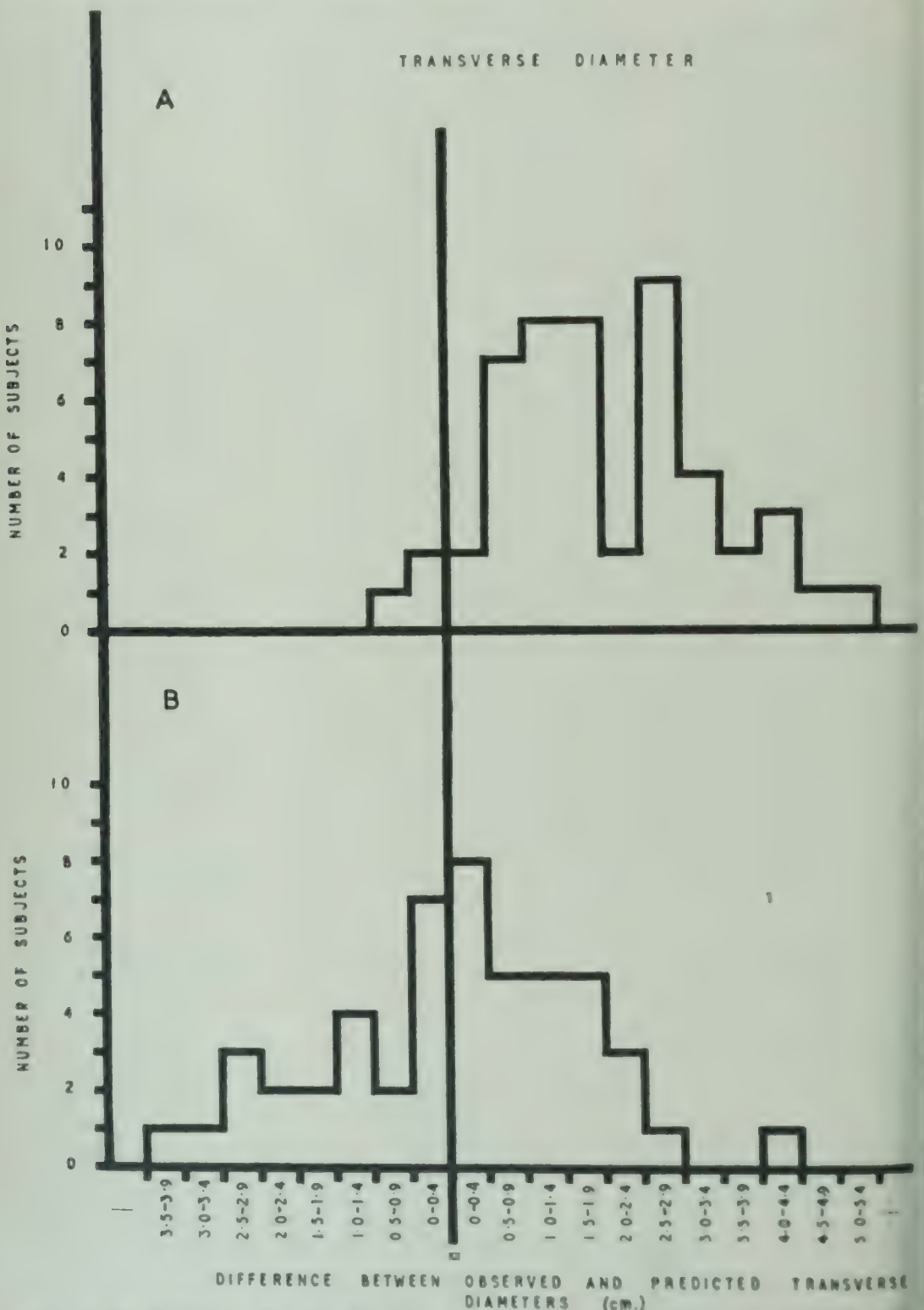

FIG. 1a. The frequency distributions among 50 undernourished German subjects of the differences between the observed measurements of the transverse diameter of the cardiac silhouette and the measurements predicted from the height and "actual" weight (A) and from the height and "previous" weight (B).

136 sq. cm. respectively) greatly exceeded the mean areas predicted from their previous weights (118 sq. cm. and 126 sq. cm.); in those subjects with pulse rates exceeding 60 beats per minute, however, the mean frontal area was almost identical with the theoretical area based upon their previous weights.

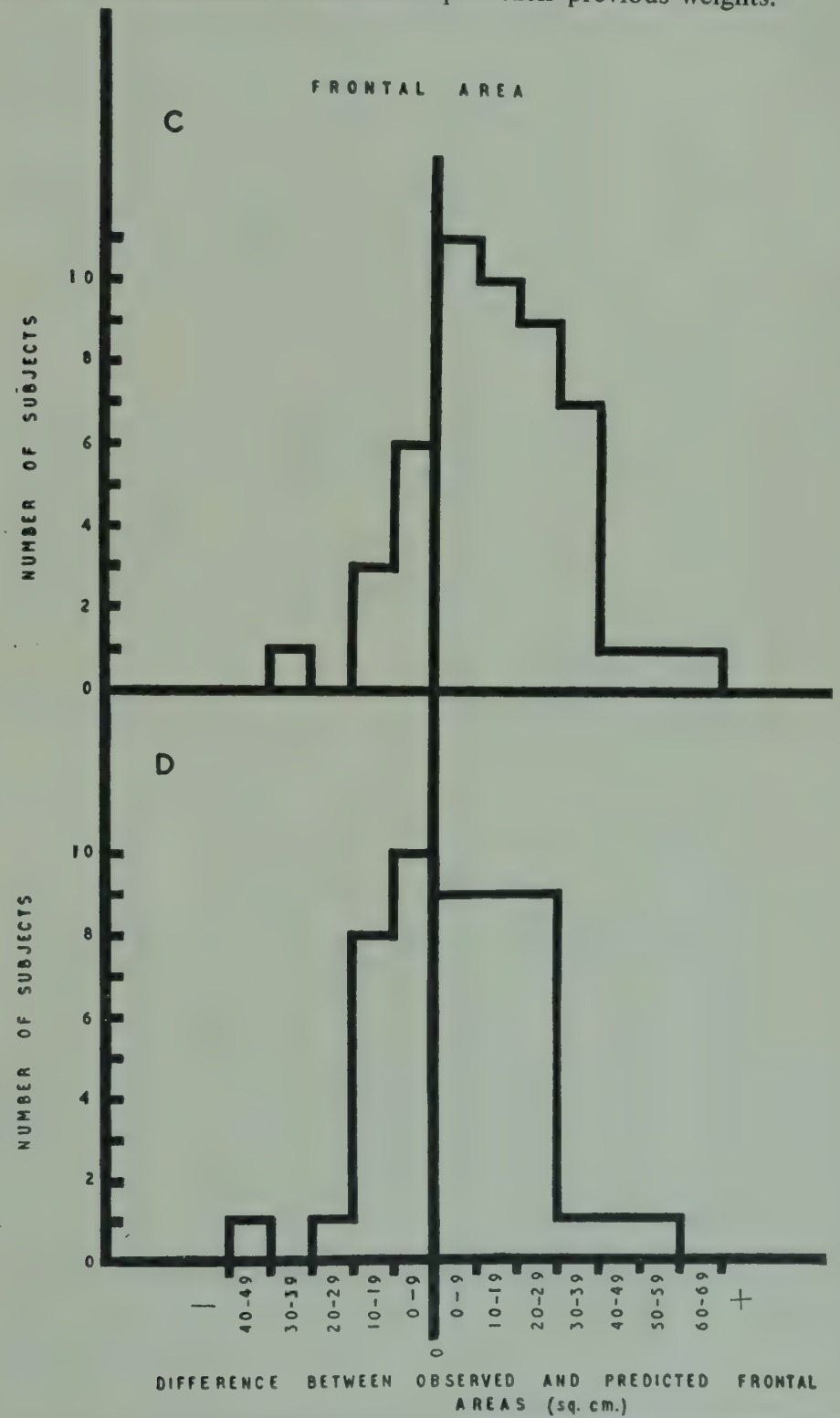

FIG. 1b. The frequency distributions among 50 undernourished German subjects of the differences between the observed measurements of the frontal area and the measurements predicted from the height and "actual" weight (C) and from the height and "previous" weight (D).

Cardiac volume. The mean cardiac volume for 19 men before they were given unlimited food was 692 c.c. (S.D. = 98 c.c.), which represented 11·8 c.c. per kg. of their actual body weights (S.D. = 1·8 c.c. per kg.) and 8·8 c.c. per kg. of their previous weights (S.D. = 1·6 c.c. per kg.) (Table 2). Liljestrand *et al.* (1939) found the mean cardiac volume of 36 well-nourished men aged 32 to 47 years to be 702 c.c., and their cardiac volume per kg. body weight to be 9·8 c.c. (S.D. = 1·3 c.c.). According to Lysholm, Nylin and Quarna (1934) the mean cardiac volume of 33 normal adults was 627 c.c. (S.D. = 122 c.c.) and the mean cardiac volume per kg. body weight of these 33 adults and 14 girls was 9·6 c.c. (S.D. = 1·2 c.c.). Thus, the mean absolute heart volume of our 19 subjects fell between the values found by Liljestrand *et al.* and Lysholm *et al.* The volume per kg. of previous weight was smaller than the figure for the normal heart and the volume per kg. of actual weight was larger. Kahlstorf (1932) gave 11·7 c.c. as the upper limit of the normal. Ten of the 19 volumes exceeded this when they were expressed per kg. of actual weight.

TABLE 2

The effect of unlimited food for eight weeks on the transverse diameter, area and volume of the heart of 19 undernourished men

Dimension	Observed measurements	
	Before	After
Mean transverse diameter (cm.)	13·9	15·0
Standard deviation (cm.)	1·0	1·3
Mean area (sq. cm.)	129	139
Standard deviation (sq. cm.)	13	15
Mean volume* (c.c.)	692	797
Standard deviation (c.c.)	98	126
Mean volume/kg. "actual" weight* (c.c./kg.)	11·8	11·5
Standard deviation (c.c./kg.)	1·8	1·8
Mean volume/kg. "previous" weight* (c.c./kg.)	8·8	10·1
Standard deviation (c.c./kg.)	1·6	1·8

*Measurements of cardiac volume are corrected for divergent distortion.

Effect of Unlimited Food for Eight Weeks on the Size of the Heart

It will be seen from Table 2 that the mean transverse diameter, frontal area and volume of the heart were all increased after eight weeks of unlimited food. These increments were all statistically significant (t = 6·4, 3·4 and 4·9 respectively, $P = <0{\cdot}01$). The mean cardiac volume per kg. of body weight, however, was not increased by refeeding, but as has been stated already the original figure was at the upper limit of the normal. The frequency distributions of these changes are shown in Fig. 2. It will be seen that the majority of the transverse diameters showed a relatively greater increase than the areas. This was because the diaphragm was in some cases from a half to one rib space higher at the end of the refeeding period, and this made the hearts slightly wider.

DISCUSSION

In assessing the significance of the cardiac measurements in this series, the following facts must be considered. Some of the subjects had been grossly

overweight before their food supplies began to fail, and since an increase in body fat should not produce an increase in the dimensions of the heart the cardiac dimensions predicted from their previous weights tended to be too high. Cardiac dimensions predicted from the actual weights of the subjects also tended

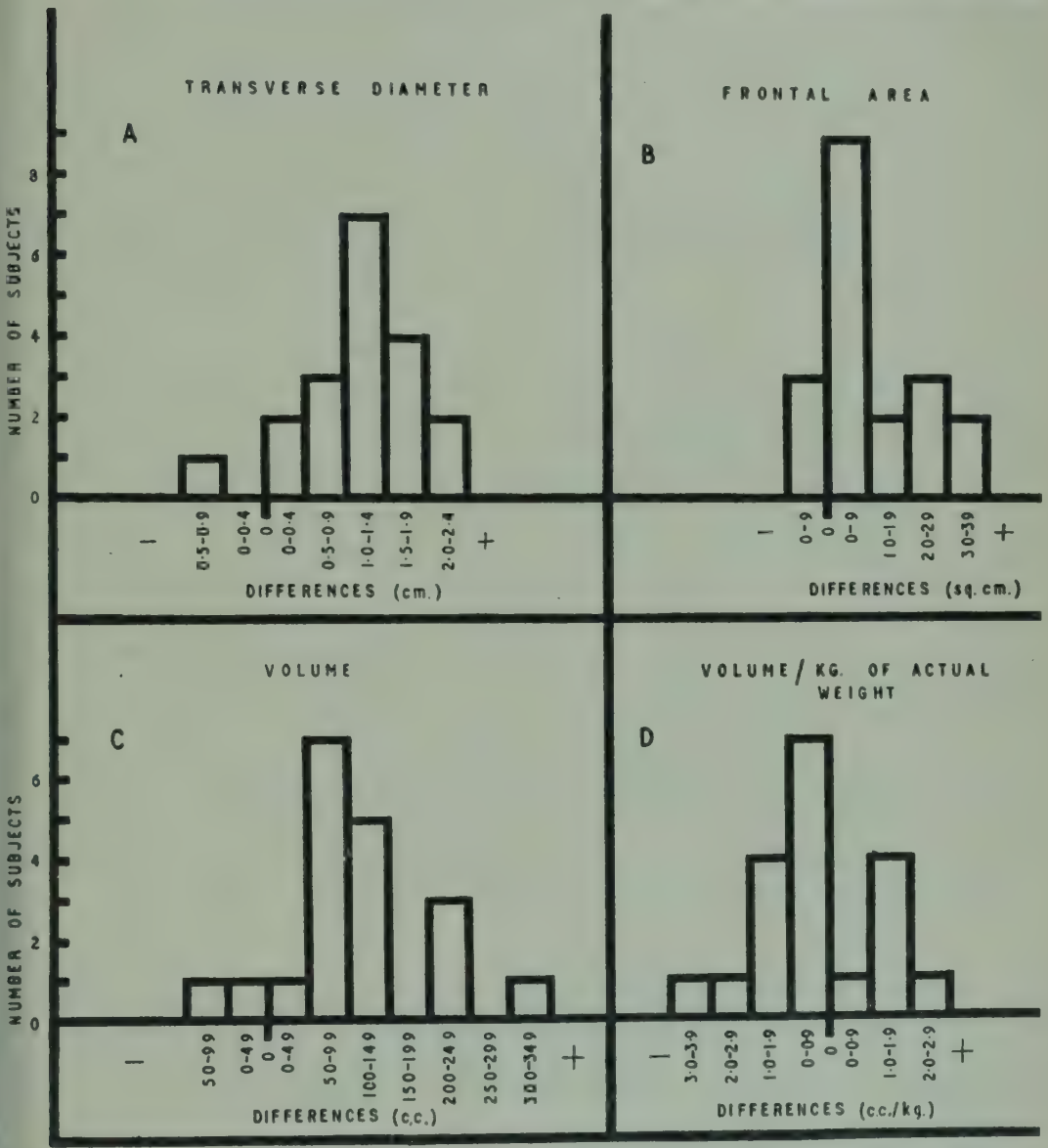

FIG. 2. The frequency distributions among 19 undernourished German subjects of the differences between the observed measurements of the heart at the end and at the beginning of 8 weeks on an unlimited diet. (A) shows the differences for the transverse diameter, (B) for the frontal area, (C) for the volume, and (D) for the volume per kg. "actual" weight.

to be too high because all the subjects probably had an excess of extracellular fluids. Neither of these sources of error, however, invalidates the present finding that the dimensions and volumes of the hearts agreed on the whole with those predicted from the subjects' previous weights, except in those subjects who had lost at least 40 per cent of their previous weights, in whom the dimensions of the hearts appeared smaller.

From the evidence given earlier, it is probable that undernourishment had reduced the weight of the cardiac musculature. The musculature occupies about a half of the total volume of the heart according to Bardeen (1918), and between

a half and one-third of the volume of the heart according to Biörck (1944). Wasting of the cardiac muscle should have produced, therefore, an appreciable decrease in the total cardiac volume. The apparent failure of the hearts of these subjects to become smaller as a result of undernourishment implies that, although there was a loss of cardiac tissue, there was an increase in the amount of blood in the heart. The diastolic heart volume depends upon the stroke volume, and the ratio between these two is constant in health in both the erect and recumbent positions (Lysholm *et al.*, 1934; Nylin, 1934). *Howarth* (p. 238) determined the stroke volume in 20 undernourished subjects by cardiac catheterization and found it to average 98 c.c., which is considerably higher than the normal value (75 c.c.). Howarth, however, examined her subjects in the reclining position, whilst the radiological observations were carried out in the erect position. It has long been known that the heart becomes smaller in the erect position. It is stated that this is due to a decrease in the amount of circulating blood, which leads to an increase in the pulse rate and a diminished stroke volume. The pulse rates found by Howarth in the reclining position were on an average only six beats per minute slower than those taken standing in the X-ray room, so that it appears justifiable to assume that the stroke volumes in the erect position were not much smaller than those found by Howarth, and the large pulsations seen on fluoroscopy in those subjects with slow pulse rates and large cardiac areas support this view. It is interesting to note that in many of the subjects the increased pulsations were only seen in the left oblique position, especially along the left ventricular contour. It may be concluded, therefore, that the large stroke volumes were responsible for the relatively large hearts found in these subjects. This agrees with the findings of Landes and Arnold (1947). There was no radiological evidence of beriberi. The mean cardiac volume after refeeding was at the upper limits of the range found in normal people by other workers, and in some individuals exceeded it. The subjects, however, had not made a complete clinical recovery at the end of this investigation. The blood volume increased after refeeding, and it is probable that the weakened cardiac musculature allowed the hearts to dilate slightly.

SUMMARY

1. The literature indicates that, as the body of an animal loses weight, the heart also loses weight, but that this loss may be relatively smaller. Similarly, post-mortem evidence suggests that in man the weight of the heart is a more or less constant fraction of the body weight regardless of the state of nutrition of the subject.

2. The hearts of 50 undernourished persons were measured radiologically. Nineteen men, who were given unlimited food for eight weeks, were examined at the beginning and end of this period.

3. The pulsations of the heart on the X-ray screen were greatest in those subjects with slow pulse rates, and in many cases the pulsations exceeded those seen in normal hearts. These increased pulsations were frequently visible only in the left anterior oblique position.

4. In the majority of the subjects the observed transverse diameters and areas of the frontal heart silhouette agreed very much more closely with those predicted from the subjects' heights and "previous" weights (i.e. before the onset of undernutrition) than with those predicted from their "actual" weights (i.e. at the time of the examination), showing that undernutrition had not diminished these dimensions.

5. Although undernutrition had probably reduced the weight of the heart itself, the volume of the heart muscle and its contents was found to be within the normal range.

6. It is suggested that this may have been accounted for by an increased stroke volume.

7. The dimensions and volume of the heart increased to the upper limits of the "normal" after eight weeks of unlimited food. This was probably because the blood volume began to increase before the musculature had recovered.

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XXII. VASOMOTOR RESPONSES TO LOCAL COLD

by M. D. Newman and P. R. V. Tomson

Some evidence may be brought forward that the blood supply to the skin is reduced in undernutrition. The hyperkeratosis and pallor (*McCance and Barrett*, p. 83), the slow peripheral bloodflow (*Howarth*, p. 238), and the lowering of the B.M.R. (*McCance and Widdowson*, p. 1; *Widdowson*, p. 313) suggest that there may be some peripheral vasoconstriction, possibly brought about by an increase of sympathetic tone.

A reaction described by Lewis (1930) and further investigated by Hertzmann and Roth (1942) was chosen for study because it was quantitatively measurable and because it took place in a relatively short time. The essentials of this reaction are as follows: when a small part of the normal human body, particularly a finger, is quickly chilled, its temperature falls rapidly to that of the environment, but after 5–15 minutes the skin becomes red and throbs, and its temperature rises by 5–20°C. After a few minutes the skin temperature falls again, and successive waves of cooling and warming take place. Lewis (1930) suggested that in the chilled tissue a histamine-like substance was produced which set up an axon reflex, dilated the peripheral vessels, and warmed the skin. Vasodilatation, however, washed away the H–substance, and vasoconstriction set in again. The latter prevailed until enough H–substance was again produced by cooling. Hertzmann and Roth (1942) have shown that the vasoconstriction was caused by a sympathetic reflex acting on the arterioles and that there was also some direct constrictor effect of cold on all the vessels of the fingers. If the sympathetic tone of undernourished people was higher than that of normal subjects, it appeared possible that some departure from the normal response to chilling might be detected.

SUBJECTS

Twenty-three undernourished German men who attended the clinic during August 1947 as applicants for extra rations on account of oedema were studied, together with 25 normal British men. The ages of the Germans varied from 18 to 61 years (average 39), and that of the normal controls from 18 to 50 years (average 28).

METHODS

The subjects sat still during the tests. The finger was immersed in a beaker of chopped ice and water, and readings of the skin temperature were taken every minute. The temperature was measured with a welded and varnished copper-constantan thermocouple attached to the pulp of the finger with sticking plaster. The thermocouple wires were connected with a millivolt galvanometer which was calibrated against a mercury thermometer before each test. The cold junction was kept in a vacuum flask filled with melting ice. The accuracy was to the nearest 0·5°C. The temperature of the water-bath was measured with a mercury thermometer and varied from 0 to 4°C. The room temperature varied from 18·5 to 26°C. on different days, but not more than 0·5°C. during any one test. The response given by each subject was expressed as the greatest difference between the temperature of the water-bath and that of the finger occurring within 10 minutes of the start of vasodilatation. If there was no warming within 15 minutes of immersion the finger was withdrawn.

RESULTS

Twenty-four tests were performed on the 23 undernourished men and 29 tests on the 25 healthy control subjects. Taking all tests into consideration, the rise of the skin temperature averaged 8°C. in the undernourished subjects (S.D. 4·5) and 11·5°C. in the controls (S.D. 5·75). The difference between the two averages was not significant statistically ($t = 1·8$, $P = 0·1$). Three controls and one undernourished man failed to show any signs of vasodilatation within 15 minutes of immersing the finger. There appeared to be no correlation between the age of the subjects and the magnitude of the rise of temperature. If only the first test done on each subject was taken into consideration, there was still no significant difference between the two groups. It was noted, however, that an increase of the room temperature usually resulted in an increase of the response given by any one subject. Table 1 gives the results obtained when tests were repeated on different days at various temperatures. If all tests were considered, there was no linear relationship between the room temperature and the response; nor was there any difference between the two groups if only tests taken at the same temperature were compared.

TABLE 1

The effects of room temperature on reflex vasodilatation

Subject	Room temperature (°C.)	Maximum rise of finger temperature above temperature of iced water (°C.)
C32	21·0	15·0
(Control)	25·0	25·5
C33	20·0	6·0
(Control) ..	24·5	11·0
C34	18·5	12·5
(Control) ..	23·0	17·0
	25·0	17·0
B217	20·5	6·0
(Undernourished)	25·0	13·0

In 12 normal subjects the nerve supply of the finger was blocked by an injection of 1 per cent adrenaline-free novocaine. In nine of these the temperature of the finger rose more, and more quickly, after the nerve block than it had done before. In one subject the block increased the speed but not the extent of the rise of temperature. In two men the response was unchanged by the block, but one was a sufferer from Raynaud's phenomenon who gave no response either before or after the injection of novocaine.

Immersion of the opposite hand in water at 5°C. or of both feet in water at 13°C. resulted in an appreciable reduction of the vasodilator response obtained from the finger. This conformed with the findings of Lewis (1931).

DISCUSSION

This investigation shows how difficult it is to compare vasomotor reactions in different individuals, and the results do not necessarily mean that the sympathetic tone was normal in undernutrition. It appears, however, that this response

might be used satisfactorily in comparing the effects of a change of conditions on the vasomotor mechanisms of one and the same person. Thus it seems that the magnitude of the vasodilatation produced by the axon reflex can be influenced by the general tone of the constrictor fibres, for the skin temperature rose less when the room temperature was lower or when another limb was cooled, and it rose more when the room temperature was higher or after a novocaine nerve block.

Since no axon reflex response was obtained from a subject suffering from Raynaud's phenomenon, even after his digital nerve had been blocked, it is probable that the peripheral vessels were unduly susceptible to the constricting effects of cold. This fits in with the views expressed by Lewis and his followers (see Richards, 1946), who thought that Raynaud's phenomenon was the result of a local defect in the blood vessels.

SUMMARY

1. Reflex vasodilatation occurring a few minutes after immersion of a finger in cold water (Lewis, 1930) was studied in 23 undernourished men and 25 healthy control subjects.

2. There was no significant difference between the responses of the two groups.

3. The response became greater as the room temperature rose, and it was increased by digital nerve block; it was reduced by lowering the room temperature or by cooling another part of the body.

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XXIII. CAPILLARY RESISTANCE AND PERMEABILITY

R. A. McCance and Lois A. Thrussell

Although workers in the first world war did not observe any abnormalities in the capillaries of the skin (Knack and Neumann, 1917) or the nail-beds (Maase and Zondek, 1917) in people who were undernourished, it has frequently been suggested that hunger oedema is due to increased permeability of the capillaries (Schittenhelm and Schlecht, 1918, 1919; Hülse, 1923; Müller, 1939; Berning, 1942; Jiménez-Diaz, Roda, Mendoza, de Landazuri, Lorente and Marina, 1942; Chabanier and Lobo-Onell, 1945; Lamy, Lamotte and Lamotte-Barillon, 1946; Strauzenberg, 1946). In spite of this it had never been demonstrated experimentally that persons with hunger oedema had capillaries with abnormally permeable walls and it seemed desirable to investigate the matter when the opportunity presented itself in Germany.

Two tests were employed. In one, measurements were made of the swelling of the forearm and hand induced by constricting the upper arm for 45 minutes with a sphygmomanometer cuff inflated to 50 mm. Hg. In the other, measurements were made of the degree of swelling produced by immersing the arm and hand in water at 0–4° C. for 1¼ hours. The first series of experiments was made in December 1946, the second in August 1947.

SUBJECTS

The undernourished subjects were selected from those who were attending the clinic at Barmen hospital as applicants for extra rations on account of hunger oedema. All had oedema except a few in the series investigated in the summer of 1947. The controls were students, doctors, convalescent patients without vascular disease at Addenbrooke's Hospital, Cambridge, and a few German prisoners of war working in England. One or two of the undernourished group had low serum proteins, which may have increased the rate of exudation from their capillaries, but on the whole the serum proteins were within the normal range. The lowest figure for serum proteins taken when the subjects were up and about was 5·06 per cent and the highest 8·0 per cent, while the average and S.D. were 6·66 and 0·685 respectively. The albumen/globulin ratios were normal.

TECHNIQUE

Cuff Experiments

A mark was made on the subject's forearm 14 cm. proximal to the styloid process of the radius with the arm held out straight. The arm was then inserted perpendicularly into a 2,000 c.c. measuring cylinder, without touching the sides until the mark was level with the 2,000 c.c. graduation, and water was slowly poured into the cylinder until the level coincided with the skin mark and the 2,000 c.c. graduation. The arm was then lifted out of the water, allowed to drip, and dried. The volume of the arm was taken to be the difference between 2,000 c.c. and the volume of water left. The sphygmomanometer cuff was applied above the elbow, the arm rested comfortably on a pillow with forearm horizontal, and a pressure of 50 mm. mercury applied quickly and maintained for 45 minutes. At the end of this time the pressure was released, the arm re-inserted into the cylinder, and the volume measured as before. It was found to be convenient to pour out about 100 c.c. of the water left in the cylinder from the previous measurements to allow for an increase in the arm volume. Changes in

volume were expressed as a percentage of the initial volume. A second series of experiments was carried out with the cuff in August 1947, using a slightly altered method of measuring the changes in arm volume. The initial volume of the arm was measured as already described. A second mark was then made on the arm, slightly higher than the first. To measure the changes the upper mark was held level with the 2,000 c.c. mark and water was poured in until the surface was level with the lower mark. The arm was then removed and the volume of water measured. This process was repeated after the cuff had been applied and removed, and the extent of the swelling obtained by deducting the second measurement from the first.

For a "lying" test the subject remained flat in bed, except for a head pillow, from 9 o'clock on the previous evening until the test was over. For a "standing" test the subject had been up and about for at least three hours before any measurements were made, but he was allowed to sit down during the test.

Cold Experiments

An arm bath was filled with water, and about an hour before the experiment ice was put in to ensure that the temperature of the water was 0°C. The whole of the forearm was immersed in the ice and water so that it could rest horizontally on the bottom of the bath. To eliminate differences in the initial volume of the arm due to posture and external temperature the first measurement was made after the arm had been in the water for five minutes. The method used for the measurement has been described in the cuff experiments. After $1\frac{1}{4}$ hours in an ice-water mixture the arm volume was again measured and the change expressed as a percentage of the initial volume.

The subject sat on a chair, with the bath, adjusted to the right level by means of wooden blocks, on a chair beside him. His arm was placed so that the edge of the bath could not possibly constrict the flow of blood to or from the hand.

TABLE 1

Effect of posture on the volume of the forearm and upon the extent to which it increased under raised venous pressure
(20 undernourished subjects)

Posture:	Lying	Standing	*t*	*P*
Average volume of forearm and hand after 3 hours (c.c.)	802	820	3·1	<0·01
Average swelling of forearm and hand under increased venous pressure (per cent of initial volume)	5·5	4·1	2·4	0·02–0·05

Effect of Posture

It was realized at the outset of these experiments that the volume of the arm and hand was likely to be affected by the posture of the arm and person before the initial measurement was made, and it was suspected from other work (Thomson, Thomson and Dailey, 1928; Waterfield, 1931; Landis and Gibbon, 1933) that the degree of swelling provoked by the tests might depend upon the

volume of the arm at their commencement. In other words, if posture had been such that some swelling had already taken place, a smaller increase might be provoked by tests subsequently applied. The matter was therefore investigated, and the results are shown in Table 1. It was clear that previous and present posture would have to be standardized in comparing the controls with the undernourished subjects. One series of subjects was accordingly investigated when they were in bed, and two when the subjects were up and about.

RESULTS

Cuff Experiments

The results of the three series of tests are shown in Table 2. No evidence was obtained that the capillaries in the arms of people with hunger oedema were more permeable than normal when the venous pressure was raised to 50 mm. Hg.

TABLE 2

Effect of undernutrition on the swelling of the forearm under increased venous pressure

Posture	Controls		Undernourished subjects	
	No.	Average swelling (per cent initial volume)	No.	Average swelling (per cent initial volume)
Lying ..	6	4·7	19	5·2
Up and about	9	5·4	20	4·1
Up and about (second series)	13	4·2	30	4·5

Confirmation of this was obtained by demonstrating that there was no correlation between the degree to which the subject's arm swelled and the grade of his oedema (see Fig. 1).

Cold Experiments

The average amount of swelling found among the five controls was 4·0 per cent of the initial volume, and among the nine undernourished people it was 3·7 per cent. Hence no evidence was obtained that the capillaries of undernourished people with oedema were unduly liable to damage by cold.

DISCUSSION

Subjects who are undernourished seldom have demonstrable oedema of the arms and hands even if they have extensive oedema of the legs. It might be suggested, therefore, that these tests should have been carried out on the lower extremities. If, however, undernutrition injures the capillary walls enough to cause oedema it is reasonable to suppose that the endothelium must be affected in the same way all over the body. If tests fail to demonstrate any injury to capillaries in the arms it is improbable that nutritional injury has been a primary cause of oedema in the legs, although the capillaries there may have become abnormally permeable for other, e.g. circulatory, reasons.

SUMMARY

No evidence has been obtained that the capillaries in the upper limbs of persons suffering from hunger oedema are abnormally permeable when the venous pressure is increased, or that they are abnormally liable to injury by cold.

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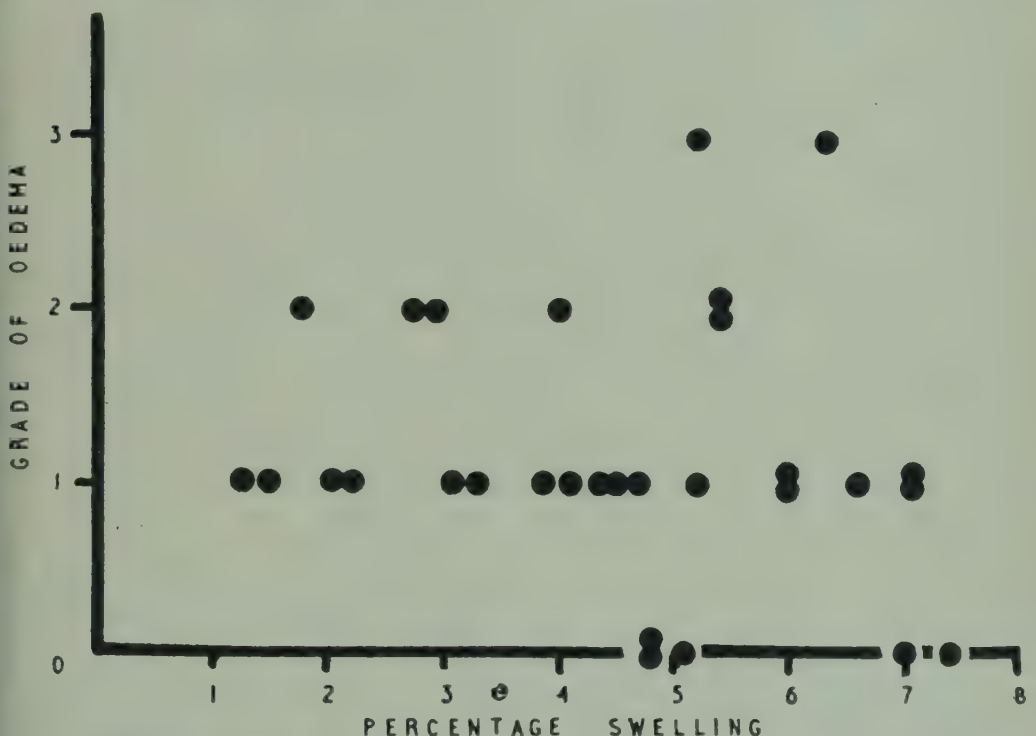

FIG. 1. Relation between the degree of swelling of the forearm under increased venous pressure and the grade of oedema in undernourished subjects.

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XXIV. RESPONSE OF THE BLOOD PRESSURE AND PULSE RATE TO POSTURAL CHANGES AND EXERCISE

by E. M. GLASER

SCHELLONG (1936) devised an exercise tolerance test which consisted of serial readings of the heart rate and blood pressure with subjects (*a*) lying, (*b*) standing, (c) lying after they had run up and down a flight of stairs. He stated that in normal persons standing was accompanied by an increased heart rate and no

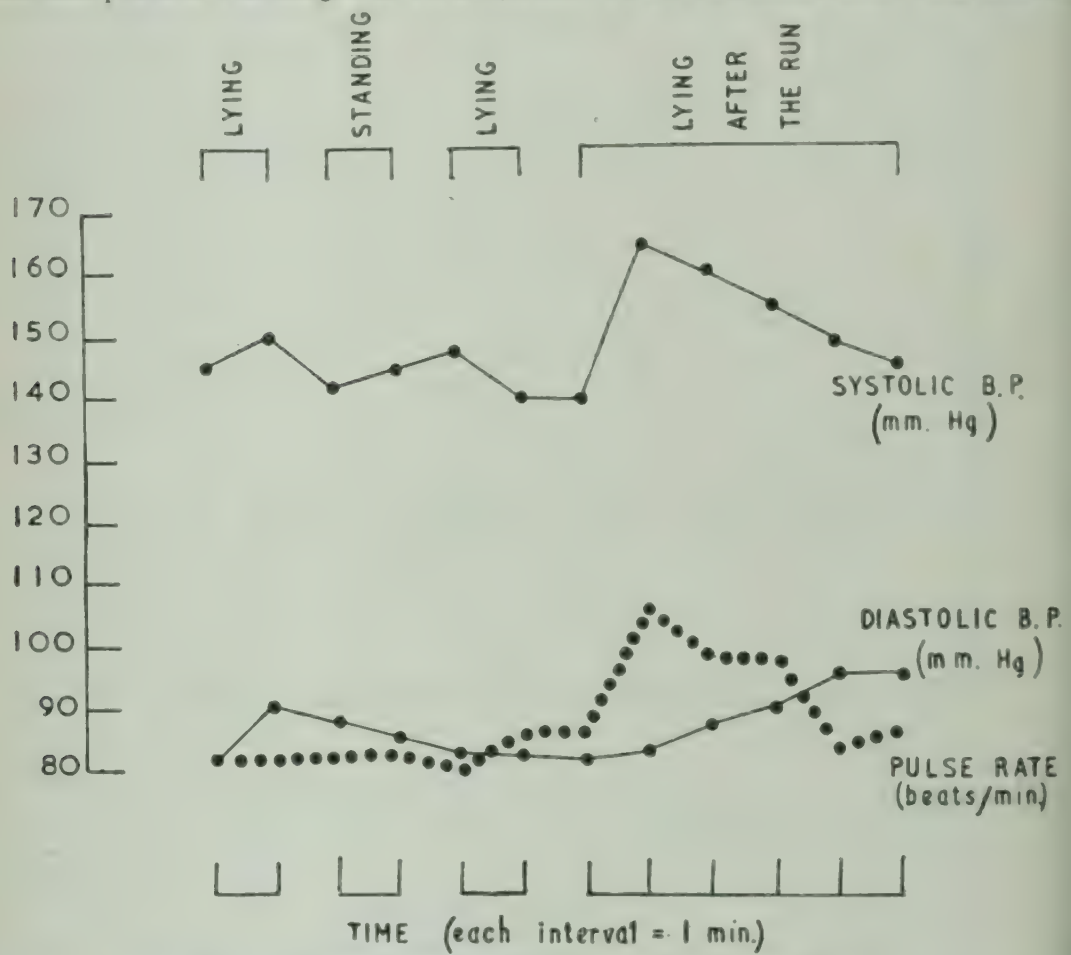


FIG. 1. "Normal" response to exercise (after Ickert, 1946).

change of the blood pressure, while exercise was followed by a rise of the heart rate and the systolic blood pressure but no change of the diastolic blood pressure (Fig. 1). Ickert (1946) used this test as a routine procedure in several thousand medical examinations, and he claimed that when food became short in Germany nearly 100 per cent of those who were undernourished responded in a characteristic way: the rise of the systolic blood pressure after the run was delayed, diminished, or absent, and the diastolic blood pressure was frequently irregular at the same time. Irregularity was not closely defined, but in Ickert's illustrations it consisted of a fall. Ickert also claimed that a change in a person's nutrition was followed by a change in his response to exercise. Thus patients who had given a normal response when they were well fed were said to have developed abnormalities when they were undernourished, but a supplement of horseflesh to their diet was said to have restored their responses to normal. Ickert thought that his findings were caused by "damage to the whole organism" and "vegetative dystonia" from lack of protein, but he only produced the records of six

observations on four subjects in evidence of his conclusions. Bansi (1949) has accepted Ickert's findings as a criterion of undernutrition.

SUBJECTS AND METHODS

Twenty-three undernourished persons were investigated, 22 men and one woman. Their ages ranged from 24 to 63 years. They were taken at random from among those who happened to be available in 1946 when these experiments were performed. In all, 25 complete tests were carried out and some of the subjects made more than one run. Eleven of the subjects were tested again after they had received a very high Calorie diet for nearly two months (*Widdowson* p. 313).

The subjects first lay down on a couch with a small pillow for 15 minutes. The initial measurements were made and the subjects then rose and stood by the couch for 2 to 3 minutes. After lying down again for a further 2 to 3 minutes they rose, walked down a flight of stairs, ran up as fast as they could and lay down on the couch once more without delay. The pulse rate and blood pressure were measured immediately after each change of posture or after the run, and at one-minute intervals in between. Blood pressure measurements were taken to the nearest 2 mm. The cuff could be detached from the mercury manometer and it remained on the subjects' arms throughout each test. The brachial artery was located and marked in the ante-cubital fossa, and all ausculations were made immediately above it. The pulse rate was taken by an assistant who counted the beats for 30 seconds. This procedure was similar to the one used by Ickert (1946).

It was found difficult to get consistent results.

1. The pulse rate noticeably slowed down while the first reading was being taken after the run. This conformed with the observations of Bowen (1903), who found that the pulse rate often returned to normal in about 10 seconds after exercise. If the pulse rate had been counted for periods shorter than 30 seconds, higher results might have been obtained immediately after the run, but new inaccuracies would have been introduced; and if the rate had been measured by a mechanical device, the variable time required to connect the subject with the apparatus might have caused errors.

2. After the run the tubes of the manometer sometimes got entangled, or the cuff slipped, or the patient lay down in a position in which it was impossible to measure the blood pressure, and no amount of forethought could completely eliminate such events. A delay of 10–15 seconds, moreover, would have been quite enough to have seriously affected the results (Rapport, 1917).

3. There were considerable variations in the amount of effort put into the run. Some subjects did their best, but others, though they seemed co-operative enough, did not really try.

4. Rising from the couch was quite an effort for emaciated, elderly, or oedematous people, and it may sometimes have resulted in a circulatory response greater than the one which should have been caused by a mere change of posture.

Neither Schellong (1936) nor Ickert (1946) have stated what variations of blood pressure they considered significant, but it was inferred from their diagrams that both disregarded changes which did not exceed 10 mm. Hg, and that Schellong thought that the normal response of the systolic blood pressure to exercise was a rise of more than 15 mm. Hg.

RESULTS

When they stood up from the couch most undernourished subjects gave normal responses by Schellong's (1936) and Ickert's (1946) criteria, but in five

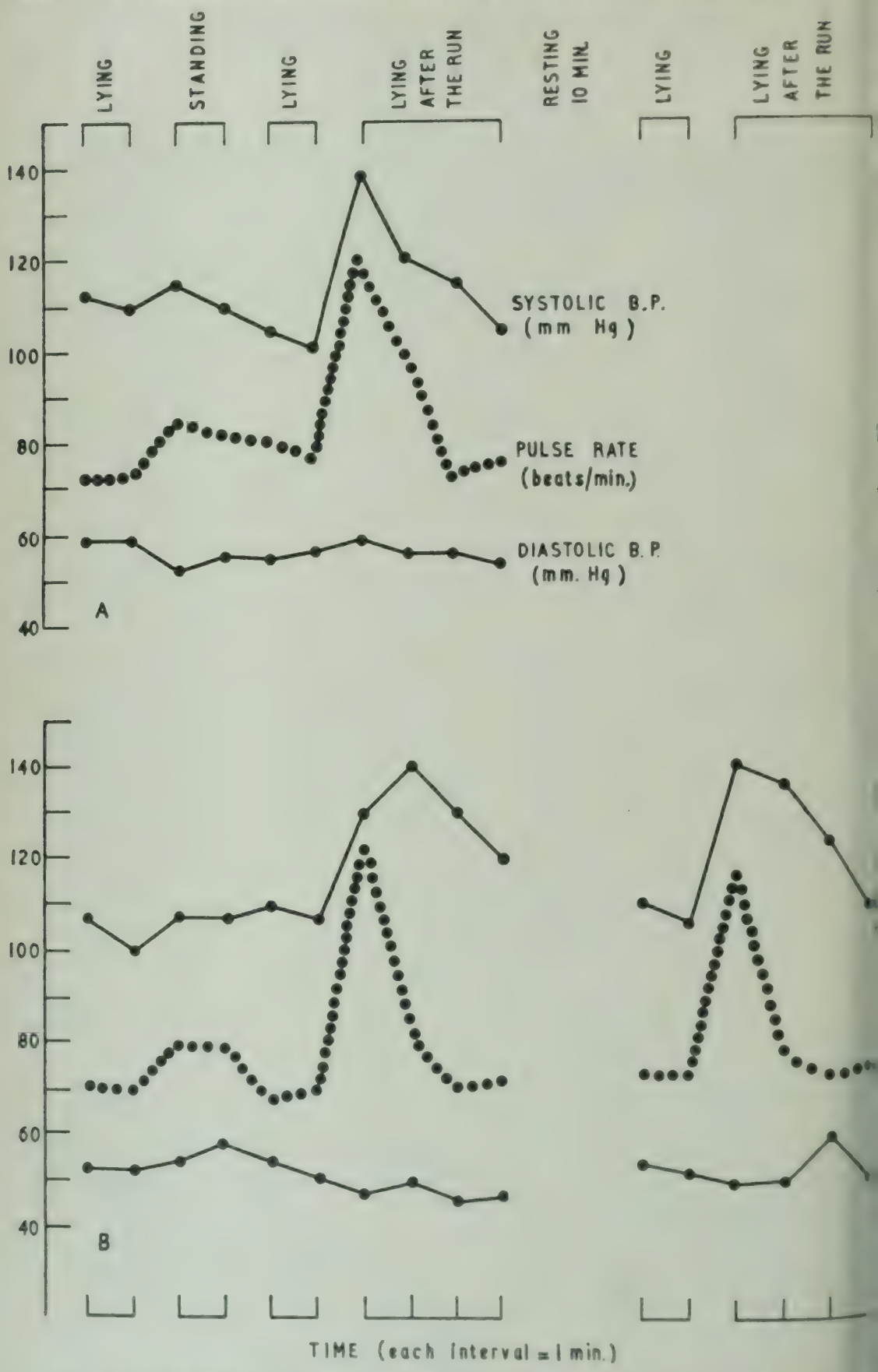


FIG. 2 A and B. Response to exercise at various stages of undernutrition and recovery. (Subject B 104, age 25, height 1·77 m.). (A) After returning from Russia (weight 69·1 kg.). (B) 4 weeks later (weight 71·7 kg.); (C) (on opposite page) a further 8 weeks later (weight 81·8 kg.).

subjects the systolic blood pressure rose by 12–20 mm. Hg, and Schellong (1936) would have considered these responses to be abnormal. As has been suggested above, the effort of getting up from the couch may have contributed to these findings. In 10 out of 30 runs performed by undernourished subjects the systolic blood pressure rose by 10 mm. Hg or less, and in the remaining runs it rose by 15–50 mm. The diastolic blood pressure varied by less than 5 mm. in 7 runs, by 5–10 mm. in 15 runs, and by more than 10 mm. in 8 runs. In one run

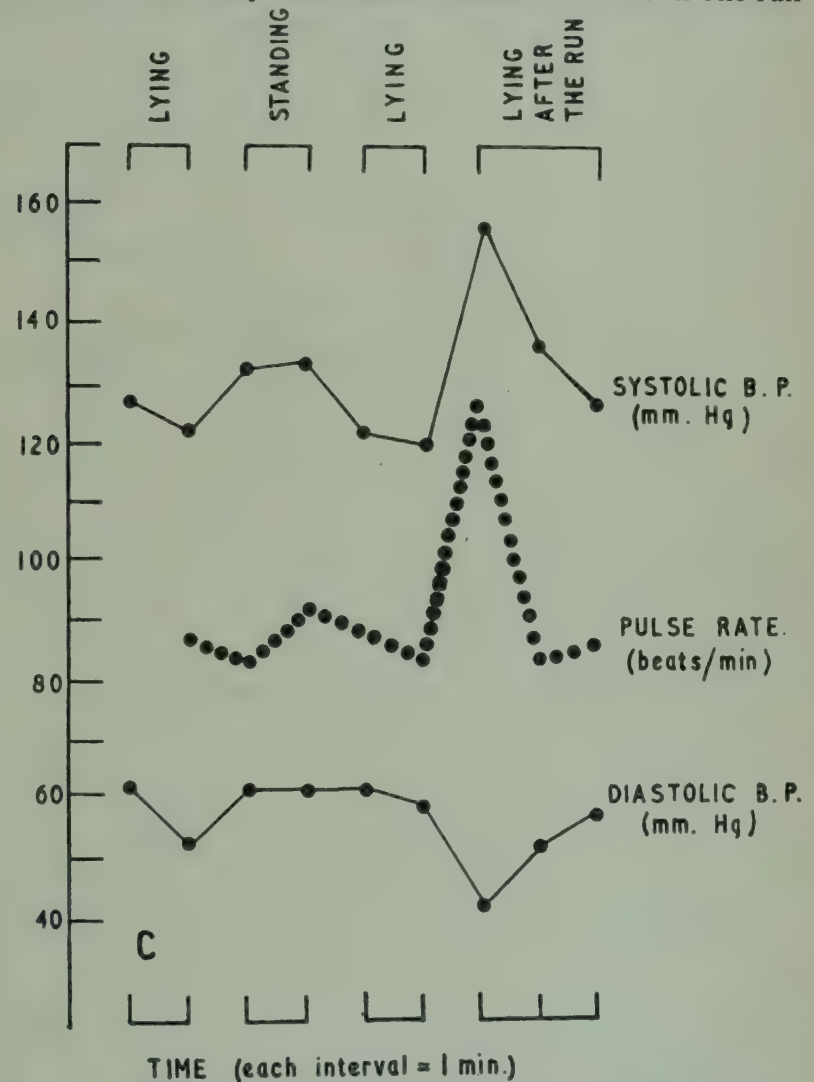


FIG. 2 C. Response to exercise at various stages of undernutrition and recovery. Same subject as (A) and (B) 12 weeks after returning from Russia (weight 81·8 kg.).

the pulse rate rose by 7 beats per minute, in 25 rnns by 10–15 beats, and in 4 runs by 51–68 beats per minute. When the results were considered in the light of Ickert's (1946) claim that almost 100 per cent of his undernourished patients showed some abnormal response to exercise, it was found that 17 tests on 15 subjects produced at least one of Ickert's pathological signs, while 13 tests on 8 subjects produced no such signs. The results obtained from the 11 subjects who took part in the feeding experiment (*Widdowson*, p. 313) show that some of Ickert's pathological signs were present in 7 subjects when they were undernourished and in 9 subjects when they were well fed; thus 4 subjects gave "normal" responses before feeding and only 2 subjects after they had had unlimited food for nearly two months.

Fig. 2 A, B, C records the responses of a subject who was repeatedly tested. The first time, when he was very emaciated, he produced a "normal" response. The

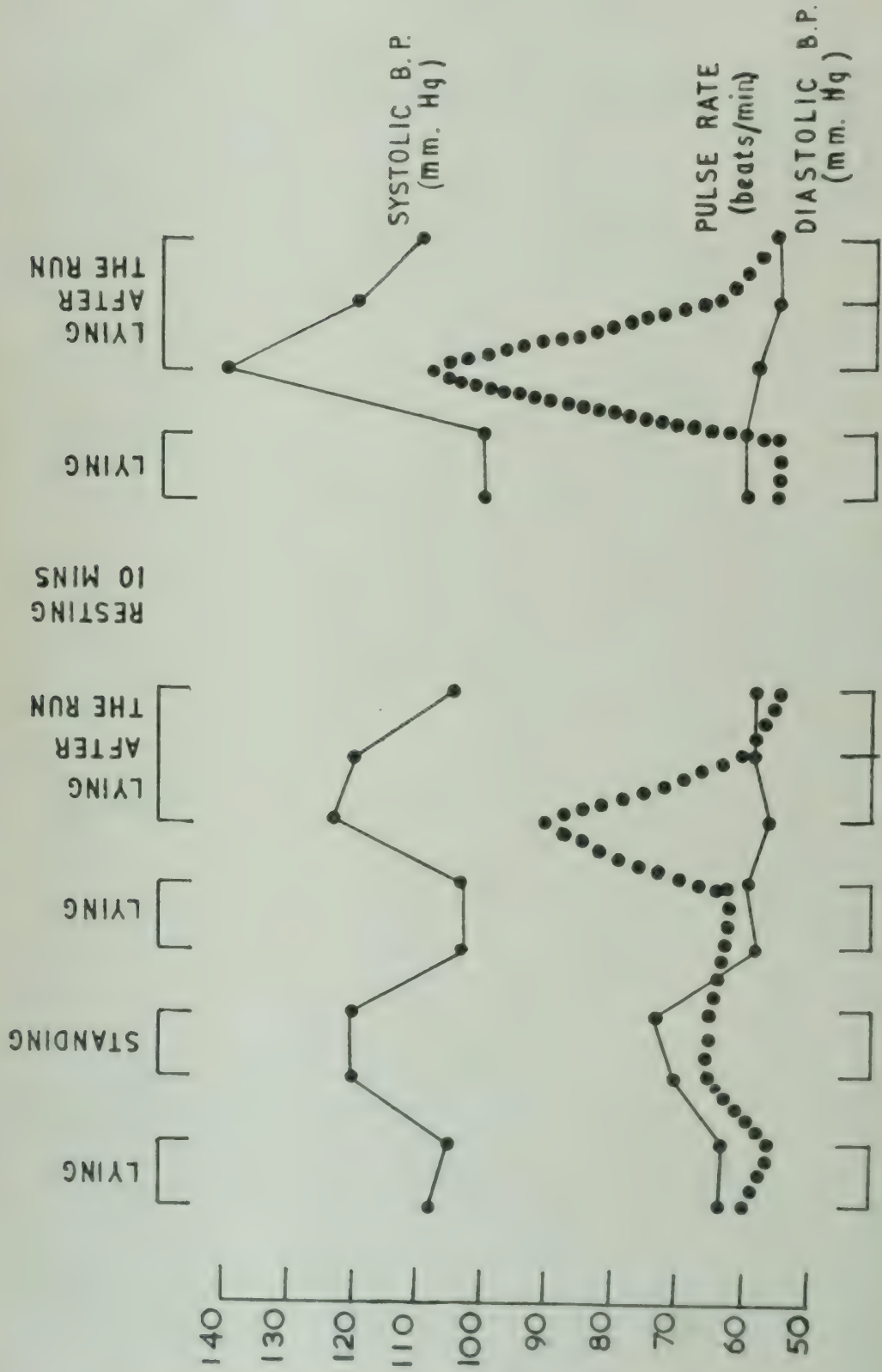


FIG. 3. Response to exercise in severe undernutrition. (Subject B 127, age 29, height 1·84 m., weight 58 kg.).

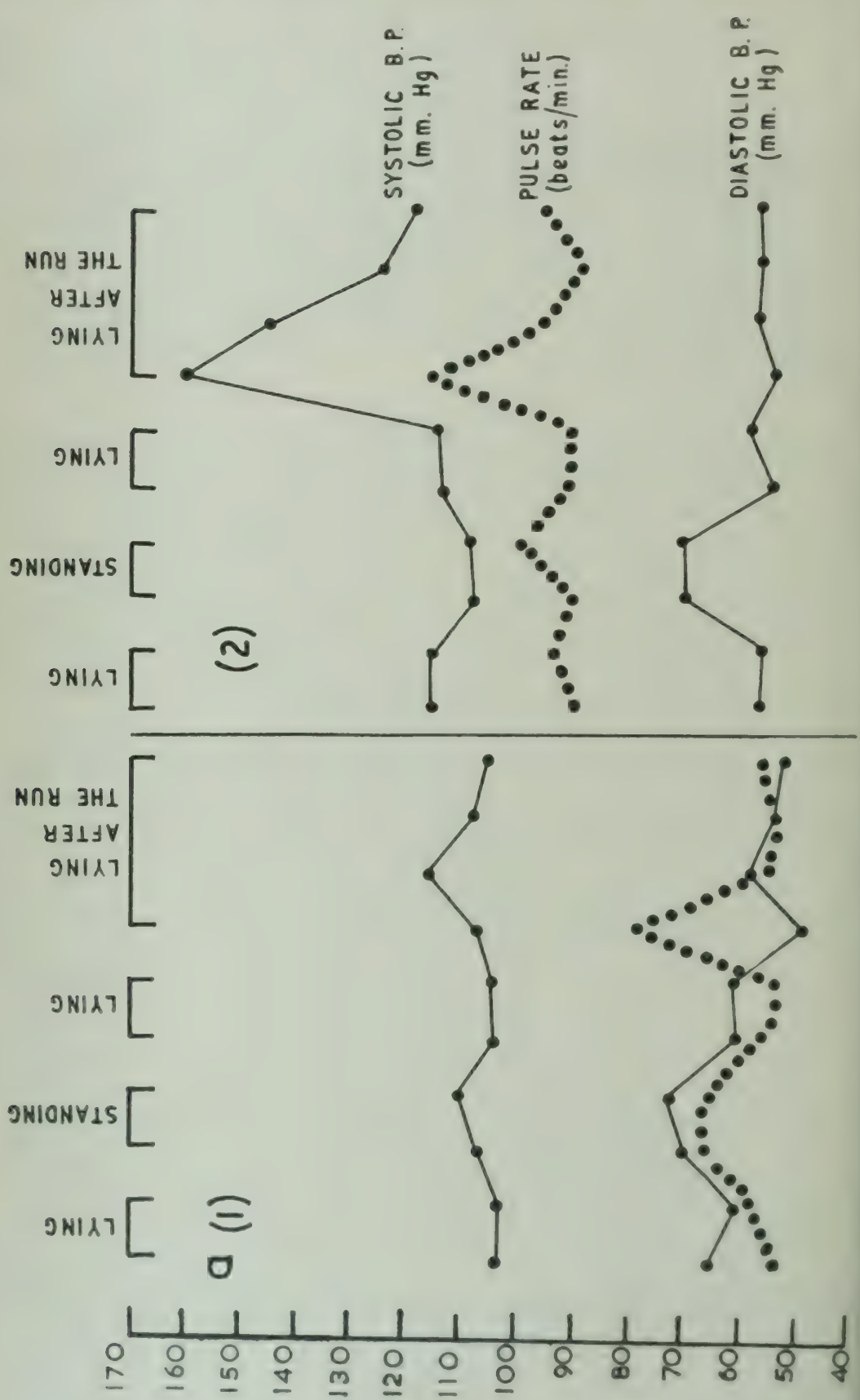
next time, when he had somewhat improved under the care of his relatives but while he was still undernourished, he did two runs and produced first a "delayed" rise of the systolic blood pressure (one of Ickert's pathognomonic signs), and then another "normal" response. Finally, he was tested at the end of *Widdowsons'* (p. 313) feeding experiment after he had gained 10 kg., and he produced a fall of the diastolic blood pressure (another of Ickert's pathognomonic signs).

Fig. 3 shows the response of a man who had been discharged from Siegburg prison on the previous day. His height was 1·84 m. and he only weighed 58 kg., but he twice produced a "normal" response to exercise. Fig. 4 gives the record of two subjects who took part in Widdowson's experiment. At its conclusion both showed a rise of the systolic blood pressure and pulse rate at rest, but in one of them (Fig. 4a) an "abnormal" response became "normal" when his state of nutrition improved, while in the other (Fig. 4b) a "normal" test became "abnormal".

DISCUSSION

Although the present investigation showed that the signs described by Ickert (1946) were present in some undernourished people, it produced no evidence that these signs were pathognomonic of undernutrition, or indeed that their presence or absence had any connexion with the subjects' state of nutrition. This is in accord with previous observations that Ickert's signs may be present in well-nourished people. A delayed rise, or no rise, in the systolic blood pressure after exercise was noted by Bowen (1904), Gräupner (1906) and Barringer and Teschner (1915). Schellong (1936) clearly stated that a delayed rise in the systolic blood pressure after exercise was compatible with a sound heart. Atzler (1938) discussed in some detail why the systolic blood pressure of normal people sometimes failed to rise after exercise, and he suggested that it might be a result of extreme effort. Rapport (1917) studied the blood pressure of human subjects by means of continuous records, and he showed that after exercise there was first a rapid fall in the systolic blood pressure, then an abrupt rise, and finally a slower return to the initial level. An investigator using an ordinary sphygmomanometer might, therefore, take the first reading when the pressure was low and the second when it had risen and so record a "delayed" rise, or he might take the first reading during the initial fall and the second when the pressure had returned to normal and so fail to detect any rise at all. The presence or absence of two of Ickert's signs would thus seem to depend on accidental factors, namely the amount of effort put into the run or the timing of the blood-pressure measurements. A fall of the diastolic blood pressure has also been frequently noted after exercise (Erlanger and Hooker, 1904; Addis, 1922; White, 1924; Bansi and Groscurth, 1930; Schellong, 1930; Mateeff and Petroff, 1931; Ellis, 1932; Schneider and Crampton, 1936; Riley, Himmelstein, Motley, Weiner and Cournand, 1948) and it may indicate some inadequacy of vasomotor control, but there is no reason to believe that it is more frequent among the undernourished than in any other group of people.

The present investigation confirmed that such tests as the Schellong test are unreliable. Rapport (1917) claimed that changes of the blood pressure after exercise could give no indication about the condition of the heart, while Addis (1922) showed that they gave no information about the peripheral circulation. At best it may be conceded that this test can give some idea of the general adaptability of a man's circulation, but its value is lessened by the fact that it disregards the respiration rate. According to Lewis (1937) " . . . of the very


SYSTOLIC B.P. (mm. Hg)
PULSE RATE (beats/min.)
DIASTOLIC B.P. (mm. Hg)
(2)
(1)
LYING
STANDING
LYING
LYING AFTER THE RUN
170
160
150
140
130
120
110
100
90
80
70
60
50
40

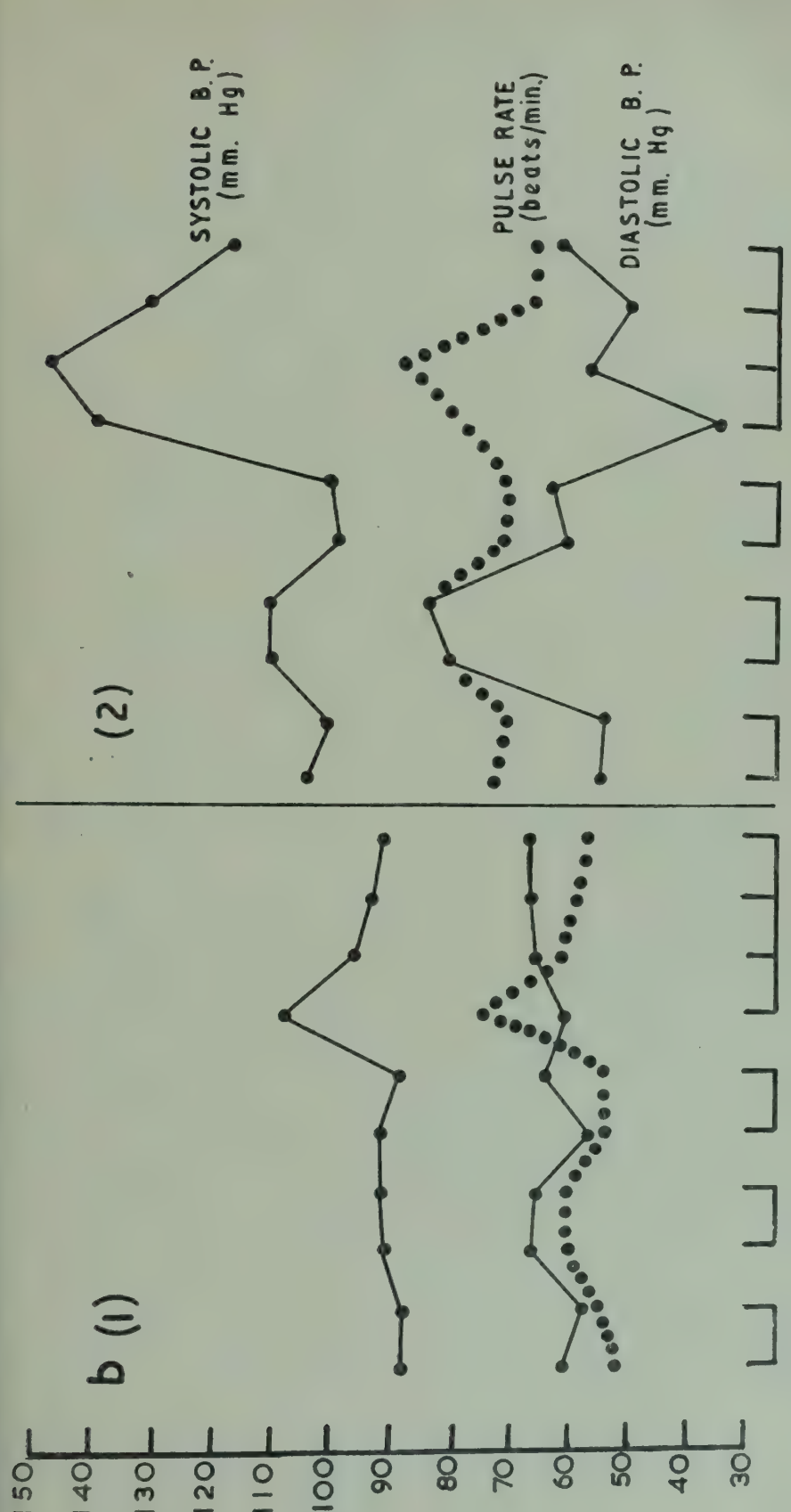


FIG. 4. Response to exercise before and after 8 weeks on an unlimited intake of food. (*a*) Subject B 72, age 57, height 1·67 m.; (1) weight 53·0 kg., (2) 8 weeks later, weight 64·0 kg. (*b*) Subject B 77, age 54, height, 1·67 m.; (1) weight 56·0 kg., (2) 8 weeks later, weight 68·0 kg.

numerous tests of cardiac efficiency and inefficiency . . . there is none that approaches in delicacy the symptom of breathlessness".

SUMMARY

1. No evidence was found in support of a claim put forward by Ickert (1946) that undernourished people gave a specific response to exercise.

2. In the light of previous writings and the present investigation, the diagnostic value of blood pressure measurements after exercise appears doubtful.

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XXV. RADIOLOGICAL OBSERVATIONS ON THE BONES

by F. R. Berridge and Kathleen M. Prior

During the later years of the first world war and immediately following it many cases of bone disease were reported which were considered to be nutritional in origin. The severity of the structural changes varied. In some patients radiological examination revealed nothing abnormal or merely some decalcification (Porges and Wagner, 1919). In other patients frank osteomalacia with severe deformities could be demonstrated. Between these two extremes, spontaneous fractures and deformities of the thorax and spine, but not of the pelvis, have been reported, mostly in women at or after the climacteric (Edelmann, 1919; Schlesinger, 1919a, b; Alwens, 1919). The radiological appearances of the bones more closely resembled those seen in senile osteoporosis than in osteomalacia. Similar bone lesions have also been seen in men and younger women (Dalyell and Chick, 1921; Hume and Nirenstein, 1921). The changes in the bones were no index of the degree of physical incapacity, for persons with no demonstrable radiological abnormalities in their bones were sometimes bedridden or only able to move about with great difficulty. Fromme (1919) described youths of 15 to 18 years with spontaneous fractures of the femora and the tibiae who had been doing heavy work in factories. The epiphysial lines of these boys showed only minor changes, and there is little doubt that these patients had "stress" or "fatigue" fractures.

In the second world war a few cases of bone dystrophy were reported from the occupied countries. Severe deformities, fractures and pseudo-fractures were reported from France, and these, like the bone changes seen in Germany during and after the first world war, were mostly in elderly women (de Gennes, Mahoudeau, Bricaire and Sénécal, 1943; de Sèze, Monnié and Ordonneau, 1943; de Sèze, Ryckewaert, Monnié and Labey, 1943; Rimbaud, Serre and Vedal, 1943); but Legrand, Warembourg, Houcke and Desruelles (1943) reported severe osteomalacia in a 32-year-old woman who was five months pregnant. In Belgium Piersotte (1945) found four elderly women and one young man who had signs of osteomalacia out of 30,000 persons examined. Burger, Sandstead and Drummond (1945) saw patients in Holland with generalized osteoporosis and progressive kyphoscoliosis, and other patients in whom radiology revealed translucent areas in the cortical zones of the bones. Pompen, La Chapelle, Groen and Mercx (1946) described 24 cases in Holland with similar radiological changes and pseudo-fractures. Not all of these, however, showed radiological osteoporosis. In Switzerland Gsell (Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948) examined 50 severely emaciated persons who had been released from concentration camps, and demonstrated slight osteoporosis in many of them. He commented upon the infrequent occurrence of true osteomalacia and suggested that the starvation had been too acute to allow time for severe bone changes to occur. Lessman (1947) reported in Germany two women with hunger osteomalacia who showed the changes in the bones described by Milkman. Bone dystrophies were probably very much rarer between 1939 and 1945 than they had been during and after the first world war, but those reported from France were of the greatest severity.

An investigation of the bones of the people in Wuppertal was carried out as described below.

MATERIAL AND TECHNIQUE

Three lines of investigation were followed:

(*a*) The health authorities were asked to send cases of bone dystrophy to the special out-patient department at the Städtisches Krankenhaus, Barmen.

(*b*) The bones of 48 persons were examined radiologically (dorsal spine 48 persons, lumbar spine 29, cervical spine 12, pelvis 13, skull 10, shoulder 26, hands 23, long bones of extremities 10). The ages varied from 22 to 80 years and averaged 47 years.

(*c*) The radiographic opacity of the calcaneum was determined by radiographic photometry in 19 German men and in 13 healthy English controls. This bone was chosen because it has approximately parallel sides, its cortex is thin, and it has a fairly uniform cancellous structure. The principle of the method was to determine the absorption of X-rays by the bone salts in a portion of the calcanei of the subjects and to compare it with the absorption by known amounts of "bone salt" in perspex boxes of standard size. Five such boxes, measuring internally 10·1 cm. in length, 10·1 cm. in depth, and 3·1 cm. in width, were used. The "bone salt" consisted of a homogeneous mixture of calcium carbonate and calcium phosphate ($Ca_3(PO_4)_2$) in the same proportion as in bone, 1 g. of the former to 9·3 g. of the latter. This was mixed with a medium which was slightly less opaque to X-rays than water to allow for the radiolucency of the fat in the bone marrow. This medium was a homogeneous mixture of sodium bicarbonate and a condensation compound of urea and formic acid, in the proportions of 7 g. of the carbonate to 5 g. of the condensation compound. The standard boxes were completely filled with the following mixtures: (1) 189·3 g. "bone salt", 15·63 g. medium; (2) 139·3 g. "bone salt", 102·5 g. medium; (3) 93·18 g. "bone salt", 154·52 g. medium; (4) 29·97 g. "bone salt", 186·23 g. medium; (5) 187·36 g. medium.

The centre of the field of the calcaneum chosen for irradiation was the centre of the rectangle formed by the superior, posterior and inferior surfaces of the calcaneum and a line parallel to the posterior surface through the posterior edge of the surface articulating with the talus. A medial radiograph was taken of the subject's left calcaneum with a metal marker on the skin in the approximate position of the central point of the field to be examined (Fig. 1). The shadow of this marker showed on the radiograph, and the distance between it and the actual centre of the rectangle was measured on the radiograph. These measurements were transferred to the living foot and the central point marked on it.

Three radio-opaque shields, 52 × 41 cm., one of lead 3 mm. thick and two of lead 2 mm. thick, each containing a circular aperture of 3 cm. diameter, were set up parallel to each other so that the apertures were in line. The X-ray tube with a cone attached to it was placed against the shield of 3 mm. lead so that the beam of X-rays traversed the apertures. This shield was 28·3 cm. from the focus of the tube. A perspex tank (length 46 cm., depth 36 cm., width 13 cm.), which was filled with water to give a constant soft tissue shadow, was placed between and in contact with the first two shields. The advantage of perspex is that it has the same opacity to X-rays as water has, and it is optically transparent. The film was placed directly behind the aperture in the third shield, which was adjusted so that the focus-film distance was 125 cm. Fig. 2).

The foot was placed on an adjustable perspex stand in the tank of water, so that the centre of the field to be irradiated was at the centre of the aperture in the lead shield, and so that the internal malleolus, the first metatarsophalangeal join-

and the upper end of the lower leg were against the side of the tank nearest the film. Three exposures of each subject were made, the foot being taken out of the tank between each exposure. The standard boxes were placed in the water tank in approximately the same position as the calcanei had occupied, and with their narrow widths (3·1 cm.) traversed by the X-rays. Three exposures were made of each box. The five standard boxes were X-rayed with each group of five subjects and the films developed together.

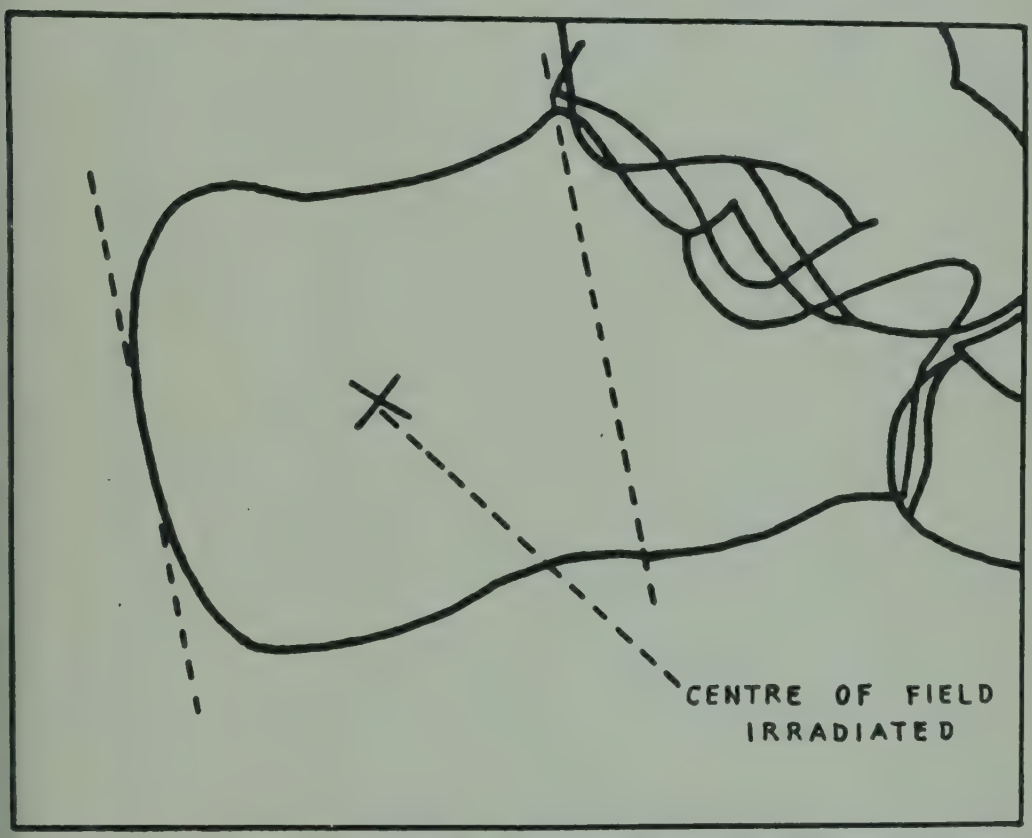

FIG. 1. Tracing of a medial radiograph of a calcaneum showing the centre of the field irradiated.

Exposures were made using the following factors: Kv 78, mA 3, exposure time 30 sec., focus-film distance 125 cm., filter 4 mm. aluminium. Kodak intensifying screens were used, and the same part of the screens was used for each subject and each standard box. The constancy of the exposures was accurate to $\pm$ 4·4 per cent.

The usual precautions required for radiographic densitometry were observed during the development of the films. The densities of the films of the standards and of the subjects' calcanei were determined by means of a photometer. The opacities of the calcanei were compared with those of the standard boxes. Histograms for both German and British subjects were constructed to show the number of calcanei whose opacities fell between the opacities of the various standard boxes (Fig. 3).

RESULTS

(*a*) No patient with osteomalacia or other bone dystrophy considered to be due to undernutrition was sent to us by the health authorities.

(*b*) The bones of the 48 persons examined did not differ in structure from the bones of a group of English people of comparable age and sex.

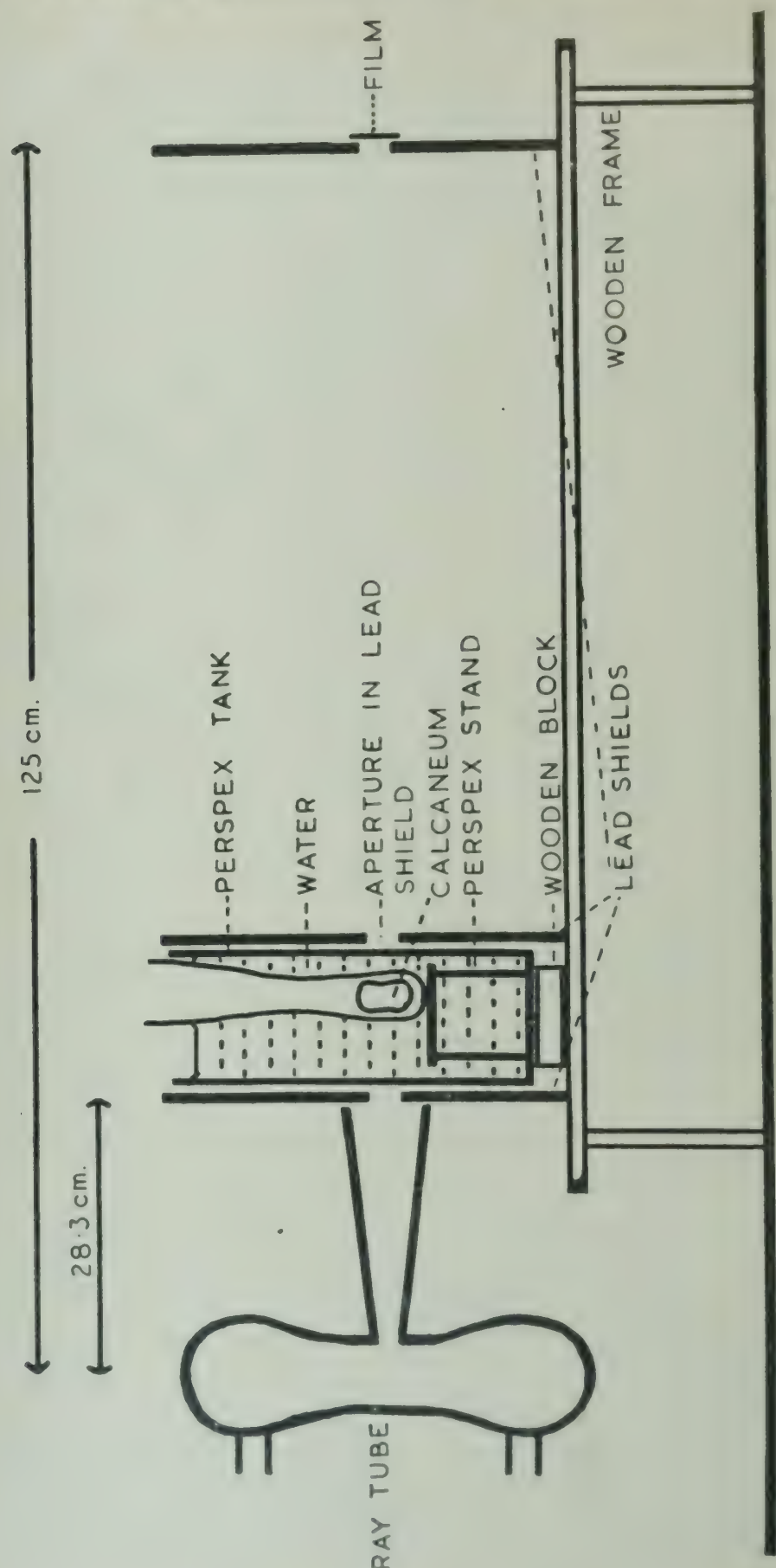

FIG. 2. Diagram of the apparatus used to determine the radiographic opacity of the calcaneum.

(*c*) It will be seen from Fig. 3 that the opacities of the calcanei of 13 of the 19 Germans were less than the opacity of box 2, but this was true of the calcanei of only 6 of the 13 British subjects. Therefore, it would appear that the calcanei of the German subjects were slightly less opaque to X-rays than those of the controls. However, when the comparison was made between the German and

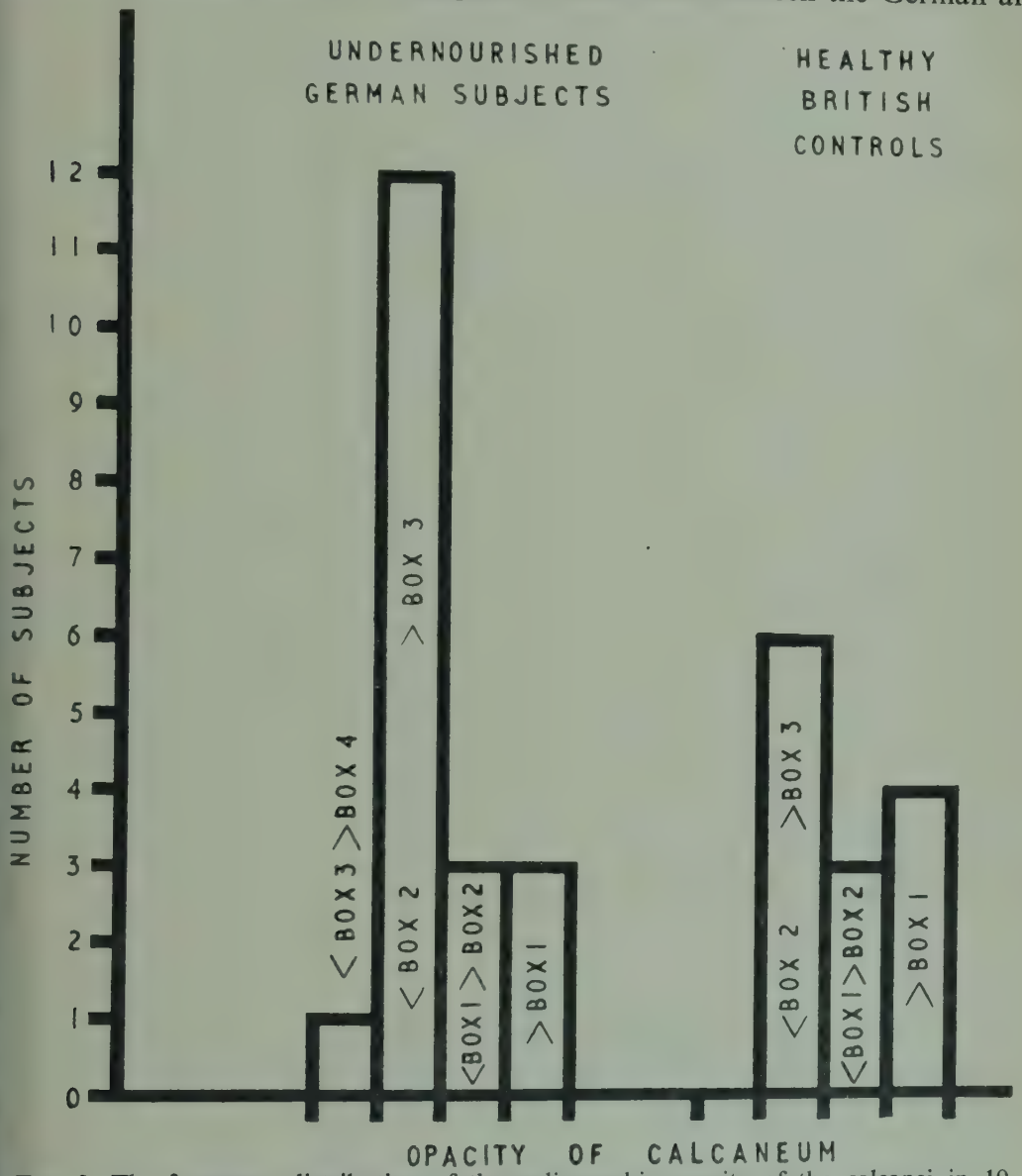

FIG. 3. The frequency distribution of the radiographic opacity of the calcanei in 19 undernourished German men and 13 healthy British controls.

British subjects by the (τ) method (Whitfield, 1947) in respect of the opacity the following results were obtained: $S = 64$, $S' = 140$, $\tau = 0{\cdot}46$, $V = 1{,}848$. The probability was therefore less than 0·1 but greater than 0·05. Thus it could not be excluded that the difference between the two groups occurred by chance. In some of the undernourished subjects and healthy controls the opacity of the calcaneum exceeded that of the "bone salt" in the first box. The amount of "bone salt" in this box had been fixed so that it was considerably more opaque to X-rays than the calcanei of three control subjects. The calcanei of these three subjects were unfortunately some of the most radiolucent found among the controls.

DISCUSSION

Bone normally contains a considerable amount of fat in the marrow and in animals this is rapidly lost in starvation and replaced by body fluid (Weiske, 1897; Sedlmair, 1899; Roger and Josué, 1900a, b). Meyers (1917) reported that the bone marrow in a man who starved himself to death in 63 days contained no fat. It is probable that this loss of fat would increase the radiographic opacity of the bones because fat is more translucent than body fluid to X-rays. Theoretically, therefore, in starvation the bones should be actually more opaque than the normal unless there is a coincident decalcification of the skeleton, and it is possible that some decalcification of the German subjects' bones was masked by a fall in the amount of fat in the bone marrow. It has never been definitely determined how much calcium must be lost from the skeleton to produce osteoporosis that could be recognized by routine radiographic methods. According to Babaiantz (1947), who decalcified sections of human vertebral bodies with 0·5 per cent nitric acid, 30 per cent of the calcium in the bones was dissolved before any change in the bones could be detected in ordinary radiographs, and 50 per cent before unequivocal evidence of osteoporosis was produced. Hinglais and Hinglais (1945) calculated that a large proportion of the population in France had lost 5 to 10 per cent of their calcium reserves annually since 1940. Coste and Berger (1945) found that the yearly incidence of osteopathy in their practices in France had increased between 1940 and 1944. The incidence had not risen uniformly from year to year, but had strikingly increased in the last two years (1940, 3 cases; 1941, 5 cases; 1942, 8 cases; 1943, 24 cases; 1944, 51 cases). If Hinglais and Hinglais (1945) were correct in their calculations, the level of decalcification in France in 1944 was from 20 to 40 per cent, which gives some support to the experimental findings of Babaiantz (1947). It would appear, therefore, that radiographs cannot be relied upon to exclude some degree of skeletal decalcification. In the present investigation no appreciable changes in the bones could be demonstrated, although the observations of *Widdowson and Thrussell* (p. 296) on the calcium metabolism of German men indicate that slow decalcification was probably taking place.

SUMMARY

1. No cases of osteoporosis or osteomalacia were discovered in Wuppertal.

2. The radiographic appearances of the bones of 48 German men and women were not found to be abnormal by routine methods of examination, but such methods probably could not be relied upon to detect slight degrees of decalcification.

3. The radiographic opacity of the calcanei of 19 German men was measured and did not differ significantly from that of the calcanei of 13 normal controls.

4. It is possible that some decalcification may have been masked by loss of marrow fat.

ACKNOWLEDGEMENTS

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XXVI. THE ABSORPTION AND EXCRETION OF NITROGEN, CALCIUM, MAGNESIUM AND PHOSPHORUS

by E. M. Widdowson and Lois A. Thrussell

The staple foods of the German people, at any rate in the towns, during 1945, 1946 and 1947 were soup made from vegetables and bread made from flour of high extraction containing no added calcium. For long periods during the winter months the adults received no milk on their ration cards, and the cheese ration was very small. Some of the German bread was made partly from rye flour, which contains an active phytase (Pedersen, 1940; McCance and Widdowson, 1944) and this bread may not have contained much phytic acid, but the main cereal used for bread-making was whole wheat. McCance and Widdowson (1942a) showed that healthy English adults did not absorb sufficient calcium from such diets to meet their requirements. Nevertheless, no case of osteoporosis or osteomalacia was discovered in the out-patient clinic (*Berridge and Prior*, p. 289), although this was one of the particular signs of undernutrition for which a special watch was kept. Furthermore, German children did grow, though not so fast as they might have done. In order to do so at all, however, they must have been in positive calcium balance. Walker, Fox and Irving (1948) suggested that if McCance and Widdowson (1942a) had carried on their experiments for a much longer time, the subjects would have ceased to be in negative balance. Walker *et al.* studied the calcium metabolism of two men continuously for eight weeks on diets containing large amounts of brown bread, and of a third for four successive weeks, and they found that, although the calcium balances were negative at first, the subjects apparently became adapted to the unfavourable dietary conditions, and gradually came into calcium equilibrium again. Others (Nicholls and Nimalasuriya, 1939) have postulated that some such process of racial adaptation must have taken place, or tropical peoples would not have survived. McCance and Widdowson (1949) did not deny this, but pointed out that the children in such countries were small, and suggested that their populations were living at a suboptimal level of calcium nutrition. How much this matters is still quite unknown, but the fact remains that millions of people must be absorbing calcium from diets in which most of the calcium is chemically insoluble. It seemed, therefore, that it would be worth while making some studies on the mineral metabolism of adults and children in Germany to try to get more insight into what regulates the amount of calcium absorbed.

Four separate studies, two on adults and two on children, have been made. The first was carried out in January 1947 on seven undernourished civilian men. The second investigation on adults was made in July 1948 on three repatriated prisoners of war six weeks after their return from Russia and on two others who had only been back for one week. The third study was made in March 1948 on five healthy boys aged 9–13 years who lived in an orphanage at Duisburg. The fourth investigation was made in October 1948 on six boys and six girls aged 9–14 years in an orphanage in Wuppertal. The object of the first three of these investigations was to study the subjects' absorption and excretion on their German diets. The fourth was of a more experimental nature and involved studies of children at two levels of calcium intake. Both investigations on children were made in the orphanages, so that the children were living their ordinary lives while their mineral metabolism was being studied. All the children appeared to be quite healthy.

The first investigation lasted for 14 days, the other three for 7 days. Samples of all foods eaten were collected and treated as described by McCance and Widdowson (1942a), and all the precautions mentioned by these authors were taken. One-tenth of each day's urine was measured out and added to the week's collection. The faeces were demarcated with carmine and the collection for the week was pooled for analysis. The week's urine and faeces were dealt with as described by McCance and Widdowson (1942a). The chemical methods which were used are described in the Appendix to this Report (p. 401).

CALCIUM, MAGNESIUM AND PHOSPHORUS METABOLISM OF SEVEN UNDERNOURISHED MEN

The men selected for this investigation were considered to be representative of those attending the out-patient clinic for extra rations on account of their undernutrition, and they either showed clinical signs of hunger oedema or were underweight. Bey. (B 160), aged 58, was the oldest. He was working as a builder's labourer and was entitled to "heavy worker" rations, which at this time provided 2,500 Calories a day when they were obtainable. He had moderate oedema (Grade 3) of his legs. Beck. (B 159), aged 54, was a pensioner from the 1914–18 war. He had a left-sided paralysis, and was not able to work, although he was able to get about. He had a trace of oedema (Grade 1) and was 14 per cent underweight according to the Hassing-Schall standards. He was receiving "normal consumer" rations, with a very small supplement of milk. Fra. (B 162), aged 53, formerly worked as a clerk at the police court, but he had been unemployed for 8 months before this investigation began. He received "normal consumer" rations and had slight oedema (Grade 2). Fel. (B 161), aged 42, was employed by the Wuppertal tramways and his job was to clean out the lines. He was entitled to "heavy worker" rations. He had no oedema but his weight was only 77 per cent of the Hassing-Schall standard. Gam. (B 163), aged 41, made artificial skins for sausages; he received "heavy worker" rations, but he was below his standard weight. Schm. (B 164), aged 32, worked in an ink factory; he received "moderately heavy worker" rations (2,000 Calories a day) and was also underweight. Sie. (B 165), the youngest, aged 29, was a labourer employed on the installation of central heating, and he was entitled to "moderately heavy worker" rations. He had some oedema (Grade 3) of his legs, but he was not underweight.

The men lived in the municipal hospital at Wuppertal-Barmen while the investigation was in progress. They were not allowed to stay in bed, and were encouraged to take some exercise in the hospital grounds. They were given the ordinary hospital diet, but their milk was limited to 100 c.c. a day and they had no cheese. Their calcium intakes corresponded as closely as possible to the amounts provided by their rations at home. Their bread was made from high-extraction wheat flour and was not fortified with calcium. They ate 750 g. of bread a day.

There was a preliminary period of four days before the metabolic balance was started, during which time the prescribed diet was eaten but no excreta were collected. The intakes and outputs of calcium, magnesium and phosphorus were then followed for two consecutive seven-day periods, and the detailed results for calcium are shown in Table 1.

As has so often been found before in experiments on human subjects, the individuals varied considerably in their ability to absorb calcium. Two of the men excreted more in their faeces than they took in their food, another two had

TABLE 1

The absorption and excretion of calcium by seven undernourished men

(Average results for 14 days)

Subjects	Intake (mg./day)	Excretion (mg./day)			Absorption		Balance (mg./day)
		Urine	Faeces	Total	(mg./day)	(as per cent of intake)	
Bey.	878	216	878	1,094	0	0	−216
Beck.	821	106	662	768	159	19	+ 53
Fel.	728	249	604	853	124	17	−125
Fra.	659	154	701	855	− 42	0	−196
Gam.	882	293	662	955	220	25	− 73
Schm.	878	215	964	1,179	− 86	0	−301
Sie.	924	148	924	1,072	0	0	−148
Average	825	197	771	968	54	7	−143

about equal amounts in the food and the faeces and three were able to absorb 17–25 per cent of their calcium intakes. Six of the seven men were in negative calcium balance, and the average loss amounted to about 140 mg. a day. These results are very similar to those obtained by McCance and Widdowson (1942a) for healthy English adults living on diets containing large amounts of brown bread, although the present negative balances were rather larger on somewhat higher intakes. The phosphorus intakes of the German men were, however, also a little higher than those of the English subjects, and the dietary calcium/phosphorus ratios were very similar for the two series (German subjects 0·29, English subjects 0·31).

TABLE 2

The absorption and excretion of magnesium and phosphorus

(Average results for 7 men for 14 days)

	Intake (mg./day)	Excretion (mg./day)			Absorption		Balance (mg./day)
		Urine	Faeces	Total	(mg./day)	(as per cent of intake)	
Magnesium	1,048	186	948	1,134	100	10	− 86
Phosphorus	2,752	1,399	1,715	3,114	1,037	37	−376

Table 2 shows the averaged results for the intake and output of magnesium and phosphorus by the seven men. All except one, Beck., were in negative balance for both elements. They absorbed about 10 per cent of their intake of magnesium on the average, and 37 per cent of their phosphorus, which was a considerably smaller proportion in both cases than the corresponding figures for McCance and Widdowson's subjects on their brown bread diets. The intakes of the Germans were, however, higher, so that the actual amounts of phosphorus absorbed by the two groups were about the same. The German men absorbed much less magnesium, although their intakes were 50 per cent higher.

These undernourished men, therefore, were behaving in very much the same way as the healthy English adults studied by McCance and Widdowson (1942a)

as regards their absorption and excretion of calcium and phosphorus, and they absorbed considerably less magnesium. Only one of the seven was able to maintain a positive balance for any of these elements, and the losses averaged 140, 86 and 380 mg. a day for calcium, magnesium and phosphorus respectively. There was no evidence that six of the seven had become "adapted" to this sort of diet, in spite of the fact that they had been living on it for nearly two years. It is possible that they had been eating at home amounts of milk and cheese, additional to the official rations, which they did not disclose, so that their calcium intakes had been higher at home than they were during the experimental period in hospital; this is, however, very unlikely. It is also possible that the allowance of bread during the experimental period was more than they had been able to obtain at home, so that their intake of phytic acid was increased, but five of the seven were entitled to "heavy worker" or "moderately heavy worker" rations, and their extra allowance was largely in the form of bread.

If Walker *et al.*'s (1948) results are recalculated in terms of calcium absorptions rather than calcium balances, several points of interest emerge. In the first place, all three of their subjects were absorbing more than 20 per cent of the calcium in their food during their first week on the experimental brown bread diet, before any adaptation could possibly have taken place. Only one of McCance and Widdowson's (1942a) subjects ever absorbed as much as this, and the average absorption of the group as a whole was 10 per cent of their intake. One of the German men absorbed 25 per cent of the calcium in his food, but four of the seven absorbed none at all, and the average absorption was 7 per cent. The calcium intakes of two of Walker *et al.*'s three subjects were reduced to half their usual amounts when the experimental régime was started, and it is a curious coincidence that they should both have been so good at absorbing calcium from the experimental diets. A higher magnesium intake would tend to encourage calcium absorption, but the magnesium intakes of Walker *et al.*'s subjects were lower than those of McCance and Widdowson's subjects on their brown bread diets, so that this is not the explanation. In the second place, L.O., one of the two subjects studied by Walker *et al.* for eight weeks, showed no sign whatever of "adaptation" for the first five weeks (called period B 1). During the last three weeks (period B 2) his calcium intake was increased by 30 per cent and at this level he was able to maintain himself in calcium equilibrium, but this is no proof that he had become "adapted" to the diet. His absorption as a percentage of his intake was the same during the last three weeks as it was during the first five. It must be concluded, therefore, that, although a large part of the world's population must be absorbing some calcium from diets low in calcium and high in phytic acid, Walker, Fox and Irving's proof of adaptation is based on slender evidence. Walker *et al.* quoted the results of other workers in support of their contention, but they themselves admitted that the results were "deliberately selected examples where the calcium balances were positive".

If it is assumed that the adult human body contains 1,000 to 1,500 g. of calcium (Mitchell, Hamilton, Steggerda and Bean, 1945; Widdowson, McCance and Spray, 1951), then a negative balance of 140 mg. a day for a year would represent a loss of about 4 per cent of the body's calcium. If decalcification of the bones cannot be detected radiologically until 30 per cent of the calcium has been lost, and evidence of osteoporosis is not certain until 50 per cent has disappeared (Babaiantz, 1947), it would take about 10 years at this rate before the loss could

be discovered by X-ray examination. Conditions in Germany had not been bad for long enough for osteoporosis to have appeared, but it is interesting that *Berridge and Prior* (p. 289) obtained some evidence of slight decalcification of the calcanei of their German subjects.

THE METABOLISM OF FIVE PRISONERS OF WAR REPATRIATED FROM RUSSIA AFTER THEIR RETURN TO A HIGH CALORIE DIET CONTAINING LARGE AMOUNTS OF BROWN BREAD

The repatriated prisoners of war from Russia all presented the same picture on their return to Germany. They were underweight, many of them had oedema, and they desired only to lie in their beds all day and to eat. They at once started

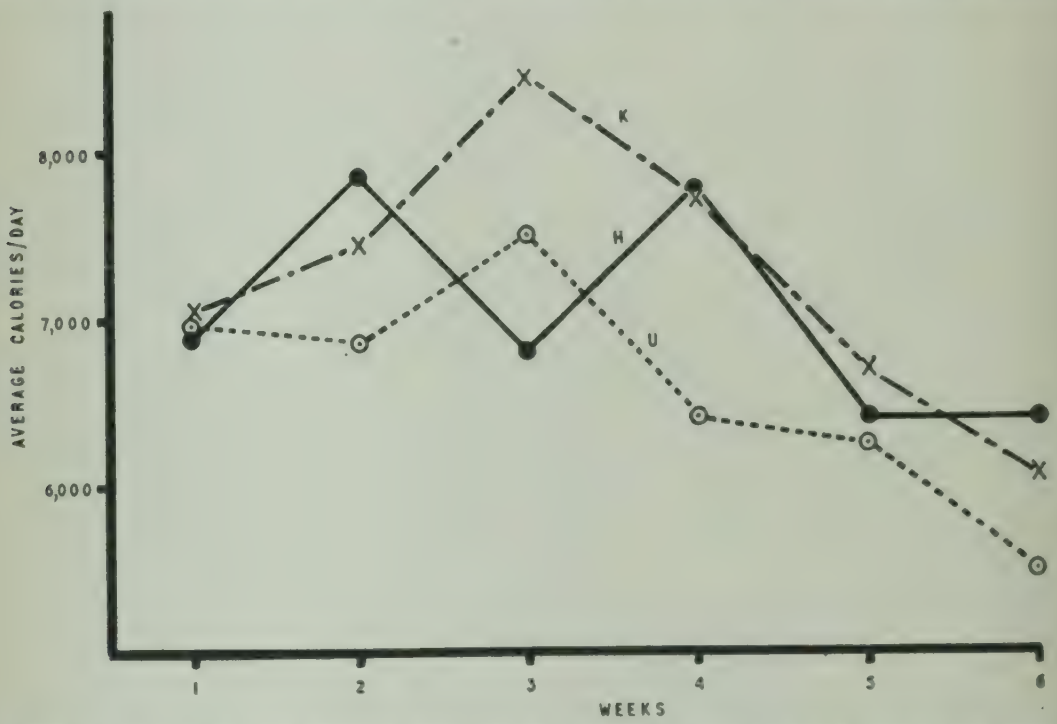

FIG. 1. Calorie intakes of three prisoners of war (H, K and U) for 6 weeks after their repatriation from Russia.

to put on weight and soon developed the enlarged parotids described by *McCance, Dean and Barrett* (p. 135). Three of these men, H. (R 39), aged 21, K. (R 40), aged 22, and U. (R 41), aged 31 years, were admitted to the municipal hospital, Wuppertal-Barmen, one week after their repatriation, and they were kept under observation for six weeks. They were allowed to do just what they wished as regards getting up or staying in bed, and they were given, in addition to the hospital diet, as much bread made from 100 per cent extraction wheat flour as they wanted, and extra jam and sugar as well. The bread was not fortified with calcium.

A record was kept of the amounts of all the different foods that each man ate during the six weeks he was in hospital, and from these records the Calorie, protein, fat and carbohydrate intakes have been calculated using McCance and Widdowson's (1946) tables of food composition. During the last week of observation the nitrogen, calcium, phosphorus and magnesium intakes and outputs were quantitatively measured, together with those of two other men, D. (R 42), aged 22, and P. (R 43), aged 25 years, who had returned from

Russia more recently and had only been in hospital for one week. These last two may therefore be considered to show an earlier stage of the recovery process, and their results will be considered separately from the other three. All the men were weighed twice weekly throughout the time they were under observation.

The Diets

Fig. 1 shows the average daily Calorie intakes of K., H. and U. over the six successive weeks of observation. K. was the biggest eater, and he reached his

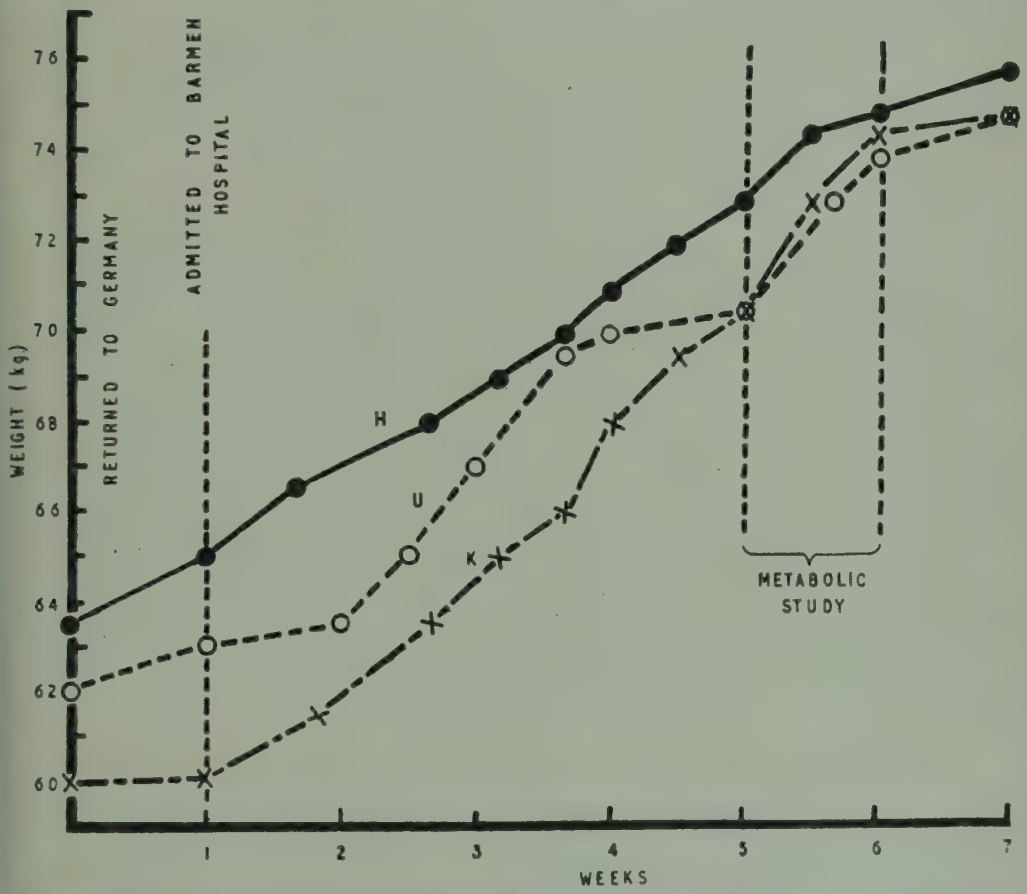

FIG. 2. Body weights of three repatriated prisoners of war (H K, and U) for 7 weeks after their return to Germany from Russia.

maximum average of 8,400 Calories a day during the third week. H. showed much more day-to-day variation than K., and he managed to eat enough food to provide him with 10,500 Calories on the last day of his second week. His overall average was 7,085 as compared with 7,244 for K. U. was older and he ate a little less than the other two. He also ate most during his third week. The appetites of all three fell off during the last two weeks of observation. Between 40 and 50 per cent of these men's Calories came from bread, and they each ate about $2\frac{3}{4}$ lb. a day. Their protein, fat and carbohydrate intakes, averaged over the whole six weeks, are shown in Table 3. The proportion of the Calories derived from protein was the customary figure of 11–12 per cent, but 78 per cent came from carbohydrate and only 10 per cent from fat. Considering the tremendous bulk of the food that these men managed to eat—9 lb. of "solid" food and 3 pints of soup a day—it is not surprising that their abdomens looked like small mountains under the bedclothes.

TABLE 3

Composition of the diets of three prisoners of war repatriated from Russia

(Averages for 6 weeks)

Subject	H.	K.	U.
Calories/day ..	7,085	7,244	6,583
Protein (g./day) ..	198	213	187
Fat (g./day)	74	76	71
Carbohydrate (g./day)	1,470	1,513	1,375
Per cent Calories from:			
Protein	11·5	12·1	11·6
Fat	9·7	9·8	10·0
Carbohydrate ..	77·8	78·1	78·4

Body Weights

Fig. 2 shows the body weights of the three men. From the time they first came back to Germany until their discharge from hospital 7 weeks later, H., K. and U. put on 12·5, 15 and 13 kg. respectively, or approximately 2 kg. a week. The fact that they had put on so much weight worried them a good deal, and they always insisted that it was "all water". How much this is likely to have been true will be seen when the metabolic balances are discussed. Both K. and U. had clinical signs of oedema (Grade 2) when they first returned to Germany, and this was unchanged after six weeks on a diet providing 7,000 Calories a day. H. had no oedema at the beginning or the end of the investigation.

These three ex-prisoners ate more food and took considerably less exercise than the nineteen men described by *Widdowson* (p. 313), and they put on more weight, but instead of looking fit healthy men at the end they appeared much too fat. Both groups had the same amount of clinical oedema at the end as at the beginning.

The Metabolic Balances

Nitrogen. The food the men (including D. and P.) were eating provided them with 30 g. of nitrogen a day during their week of metabolism (Table 4). This figure agrees very well with the calculated amount of protein in the diet during that particular week.

They absorbed 75–80 per cent of this nitrogen and retained 12 g. a day, or more than 40 per cent of their intake. Assuming cells to contain 67 per cent of water, the average retention of nitrogen during the week amounted to 1·62 kg. of cell mass. The average gain in weight over the whole six weeks was 2 kg. a week, but the average increase was 3·2 kg. during the week when intake and output were being measured, so that approximately half the gain in weight was due to muscle and about half to fat. *Widdowson and McCance* (p. 165) and McCance and Widdowson (1951) came to a very similar conclusion after studying the distribution of body water in another group of repatriated men. Beattie, Herbert and Bell (1948) followed the intake and excretion of nitrogen by 6 Dutch subjects in 1945, after the liberation of Western Holland, and of 11 German subjects in 1946. The nitrogen intakes in the Dutch investigation were of the same order as those of the ex-prisoners of war here described, but their Calorie intakes were much lower and the proportion of Calories derived from protein was of the order of 40 per cent on the high-protein diet and 22 per cent

TABLE 4

The absorption and excretion of nitrogen, magnesium and phosphorus by five prisoners repatriated from Russia

(Average results for 7 days)

	Intake	Excretion			Absorption	Absorption (as per cent of intake)	Balance
		Urine	Faeces	Total			
Nitrogen (g./day) 3 men sixth week after return ..	29·3	11·2	6·0	17·2	23·3	79·5	+ 12·1
2 men second week after return	30·1	9·8	7·7	17·5	22·4	77·6	+ 12·6
Magnesium (mg./day) 3 men sixth week after return	1,630	167	957	1,124	673	41·4	+ 506
2 men second week after return	1,688	205	766	971	922	54·6	+ 717
Phosphorus (mg./day) 3 men sixth week after return	5,762	1,907	2,352	4,259	3,410	59·2	+1,503
2 men second week after return	5,700	1,696	1,943	3,639	3,757	65·9	+2,061

TABLE 5

Calcium metabolism of five prisoners of war repatriated from Russia

(Average results for 7 days)

Subject	Intake (mg./day)	Excretion (mg./day)			Absorption		Balance (mg./day)
		Urine	Faeces	Total	(mg./day)	(as per cent of intake)	
Sixth week after return							
H.	1,754	40	1,229	1,269	525	30·0	+485
K.	1,766	144	1,643	1,787	123	7·0	− 21
U.	1,720	166	1,471	1,637	249	14·5	+ 83
Average	1,747	117	1,447	1,564	300	17·2	+183
Second week after return							
D.	1,754	200	867	1,067	887	50·7	+687
P.	1,774	264	1,066	1,330	708	39·9	+444
Average	1,764	232	967	1,199	797	45·3	+565

on the low. On these diets the Dutch subjects, who had clearly all lost a great deal of weight, retained 5–10 g. of nitrogen a day. It would be interesting to know if their retention would have been higher if they had had more Calories and the same amount of nitrogen in their diets.

Calcium. The three men who were studied during the sixth week after their return to Germany behaved very differently among themselves as regards their absorption and excretion of calcium and it is difficult to generalize about them (Table 5). Their calcium intakes were high because they ate so much food. All absorbed some calcium, so that their average absorption was considerably higher than that of the civilian men. H. managed to absorb enough to enable him to retain nearly half a gram a day, K. was in small negative, and U. in slight positive, balance. The calcium/phosphorus ratio in their diets was 0·30, which is very nearly the same as that in the diets of the civilian men already described. Their diets contained twice as much phosphorus as well as twice as much calcium as those of the civilian men. D. and P., who had only been back from Russia for one week when the metabolic balance was started, both absorbed considerably more calcium than any of the other three men from similar diets. The difference may have been due to individual variations in the ability to absorb calcium. It should be noted that D. and P. absorbed and excreted almost exactly the same amounts of nitrogen as H., K. and U.

It is clear that the capacity to absorb and retain calcium from diets containing a high phytic acid/calcium ratio is not peculiar to childhood. The repatriated prisoners put on weight because they ate so much food, and there is no reason to suppose that the civilian men would not have done the same, and been in positive calcium balance, had they been given diets providing them with 7,000 Calories and 1·7 g. of calcium a day. Whether the 7,000 Calories or the 1·7 g. of calcium was the deciding factor, or whether it was the state of nutrition of the repatriated prisoners, cannot be stated with certainty, but it is suggested that the absolute amount of calcium in the diet is very important in regulating the amount of calcium absorbed. These results will be discussed further when the findings for the children have been presented.

Magnesium and phosphorus. Table 4 shows the average results for the absorption and excretion of magnesium and phosphorus by the two groups of men. All the men showed high absorptions and positive balances for both elements, and the results for magnesium are similar to those for calcium in that the two men studied soon after their repatriation absorbed and retained considerably more than the three who were investigated at a later stage. The results for phosphorus for the two groups also show a difference in the same direction, but to a smaller degree.

THE ABSORPTION AND EXCRETION OF NITROGEN, CALCIUM, MAGNESIUM AND PHOSPHORUS BY FIVE BOYS LIVING ON THE GERMAN RATIONS

It has long been recognized that if children are in a poor state of calcium nutrition they will absorb and retain more calcium from a given diet than children who are well nourished as regards this element. Children in Germany were undoubtedly undernourished, and the present study has no bearing whatever on the requirement of healthy children for calcium. Its object was to see how much calcium, magnesium, phosphorus and nitrogen German children were able to absorb from the rations they were receiving, and to compare the

findings with those already described for two groups of adults living on diets similar in composition though different in quantity, and with the results of other workers for children in a good state of calcium nutrition.

The boys taking part in this investigation were living in an orphanage where a dietary experiment was in progress, but these particular children were not involved. They benefited, however, because they received extra milk and bread from the rations not required for the children on the experimental diets. Apart from this they ate only the normal rations of foodstuffs according to the scale in force at the time. Their bread was made from 100 per cent extraction wheat flour which was not fortified with calcium, and they ate about 600 g. a day. They were not receiving any supplementary vitamin D. Table 6 gives some

TABLE 6

Heights and weights of boys taking part in the metabolic balance

Name	Age (years and months)	Weight as percentage of of "standard"	Height as percentage of of "standard"
Bruno	9·8	80·7	90·0
Otto	11·3	94·4	92·8
Manfred	11·5	91·3	89·7
Joseph	13·1	110·2	103·1
Horst	13·2	89·2	89·7
Average		93·2	93·1

details about their weights and heights; all but one were short and light for their ages according to the tables of O'Brien, Girshick and Hunt (1941).

Table 7 shows the amount of calcium in the food and excreta of the five boys, Table 8 their average intakes and outputs of nitrogen, magnesium and phosphorus, and Table 9 their intakes and excretions of phytic acid phosphorus.

TABLE 7

The absorption and excretion of calcium by five boys living on the German rations

(Average results for 7 days)

Subject	Intake (mg./day)	Excretion (mg./day)			Absorption		Balance (mg./day)
		Urine	Faeces	Total	(mg./day)	(as per cent of intake)	
Bruno ..	704	19	471	490	233	33·2	+214
Otto ..	944	43	509	552	435	46·1	+392
Manfred	951	111	553	664	398	41·8	+287
Joseph ..	1,017	55	633	688	384	37·8	+329
Horst ..	1,021	162	664	826	357	34·8	+195
Average ..	927	78	566	644	361	39·0	+283

The results are much more uniform from one child to another than they were for either of the groups of adults already discussed. The children had, on the average, 0·93 g. of calcium a day in their food, of which they absorbed 39 per cent, although their diets contained 0·8 g. of phytic acid phosphorus a day,

and the calcium total phosphorus ratio was only 0·35. They were in need of calcium for growth, and they were able to absorb and retain considerable amounts in spite of the fact that the quantities of phytic acid in their diets were very high. Hoff-Jørgensen, Andersen and Nielsen (1946) have described the results of metabolic studies for 15 days on two boys of 10 years whose diets also contained 0·93 g. of calcium a day. They were eating bread made from high extraction wheat and rye flour, and oatmeal porridge, and

TABLE 8

The absorption and excretion of nitrogen, magnesium and phosphorus

(Average results for five boys for 7 days)

	Intake	Excretion			Absorption	Absorption (as per cent of intake)	Balance
		Urine	Faeces	Total			
Nitrogen (g./day) ..	14·42	8·91	3·29	12·20	11·13	77·2	+ 2·22
Magnesium (mg./day) ..	880	110	650	760	230	26·7	+ 120
Phosphorus (mg./day) ..	2,600	1,130	980	2,110	1,620	61·8	+ 490

TABLE 9

The intake and output of phytic acid phosphorus

(Average results for 7 days)

Subject	Phytic acid phosphorus		
	In bread (mg./day)	In faeces (mg./day)	Percentage broken down
Bruno	620	14	98
Otto	737	15	98
Manfred	744	15	98
Joseph	943	50	95
Horst	969	36	96
Average	803	26	97

their diets contained 0·48 g. of phytate phosphorus a day and had a calcium total phosphorus ratio of 0·45. These children had been in hospital for about three months before the beginning of the investigation on account of bronchial asthma, and had been having plenty of calcium and vitamin D and very little phytic acid during this time. In the experimental high-phytic acid period these two boys absorbed only very small amounts of calcium, which amounted to 1 and 5 per cent of their intakes respectively, although their diets contained little more than half as much phytic acid as our children's. One was in slight negative and one slight positive balance over the 15 days, but neither appeared to have been retaining calcium as he should. Both boys were in slight negative calcium balance during the first five-day period and slight positive balance afterwards, and Hoff-Jørgensen, Andersen and Nielsen themselves, and also Walker *et al.* (1948), interpret this as an "adaptation" to unfavourable dietary conditions

Unless children adapt themselves much more rapidly than adults it is strange that they should have become "adapted" after five days, since McCance and Widdowson's (1942a) subjects showed no signs of it after 21 days, and Walker *et al.* considered that much longer than this was required. There appears to have been only a one-day interval when changing from the low-phytic acid to the high-phytic acid diet, and the results for the first five-day period may well have been influenced by the previous dietary régime.

Macy (1942) summarized the results of 593 five-day metabolism experiments on 29 well-nourished children between 4 and 12 years of age. Their diets contained little or no phytic acid and the calcium/phosphorus ratio in them was 0·74. On an average calcium intake of 0·93 g. a day, 30 per cent was absorbed and 20 per cent retained. Our children, therefore, absorbed and retained even more calcium than the American children, and far more than the Danish ones, although their diets were much the most unfavourable of the three for calcium absorption. The body's needs for calcium and the previous level of intake are of fundamental importance in determining the amount of calcium that will be absorbed. Table 9 shows that 97 per cent of the phytic acid in the German children's food had been hydrolysed, whereas only about two-thirds of the phytic acid in Hoff-Jørgensen *et al.*'s two Danish boys' diets was broken down. This fact explains, on chemical grounds, how the German children were able to absorb so much more calcium, but one would like to know what difference there could have been in the conditions inside the intestines of the two groups of children to enable those who needed most calcium to break down most phytic acid. This point will be discussed further when the next investigation has been described.

The five German boys were retaining considerable amounts of nitrogen, magnesium and phosphorus as well as of calcium (Table 8). The ratio of the quantities of calcium and nitrogen retained may be taken as an indication of the proportions of bony and muscular tissue being laid down. For Macy's children of 9–12 years this retention ratio $\frac{Ca \times 100}{N}$ was about 20, the corresponding figure for the German boys was 12·8, for the two ex-prisoners of war recently returned to Germany 7·9, and for the three men who had been back from Russia for six weeks 1·5.

THE EFFECT ON CHILDREN'S MINERAL METABOLISM OF ADDING CALCIUM CARBONATE TO THEIR BREAD

It has been shown (McCance and Widdowson, 1942a) that if calcium carbonate is added to the diet of healthy adults who are eating large quantities of brown bread they will absorb more calcium, and it was partly on the basis of these findings that it was decided to fortify the "National loaf" with calcium.

The German children just described appeared to be absorbing quite large amounts of calcium from diets from which well-nourished children or adults would probably have absorbed little or none, and it was decided to make a further study of German children at two levels of calcium intake. An orphanage in Wuppertal, where there were about 60 children between 4 and 14 years of age, was selected for this investigation. On the basis of their age, sex, height and weight, and clinical condition the children were divided into two groups which were as equal as possible in every way. They were given their ordinary German rations, and all their bread was made from 100 per cent extraction wheat flour. The bread of one group was not fortified in any way; that of the other was made from the same flour containing 1 per cent of calcium carbonate, so that

the final bread contained about 300 mg. of added calcium per 100 g. None of the children received supplementary vitamin D. After four months of this régime the mineral metabolism of three boys and three girls from each group was studied while they continued to eat the diet to which they had become accustomed. The detailed results on all the children in the home, and the effect of the added calcium on their growth in height and weight and on their clinical condition will be described in a later publication. Table 10 gives some data

TABLE 10

Description of children taking part in the metabolic balance at two levels of calcium intake

Name	Sex	Age (years and months)	Weight as percentage of of "standard"	Height as percentage of of "standard"
Group A	Bread	containing	*no* added calcium	
Else	F	11·5	73·6	92·2
Inge	F	11·10	108 4	97·8
Christel	F	13·10	77·0	96·7
Wolfgang	M	10·6	87·8	93·8
Herbert	M	12·0	99·7	99·2
Adolf	M	12·1	93·1	98·3
Average			89·9	96·3
Group B	Bread	containing	added calcium	
Sigrid	F	9·3	95·8	94·0
Margot	F	11·3	88·5	98·6
Marlies	F	13·1	70·5	90·2
Harald	M	9·11	104·0	101·5
Horst	M	11·7	80·5	92·8
Lothar	M	12·3	87·5	95·0
Average			87·8	95·3

about the twelve children selected for the metabolic study. These children were short and light for their ages according to the American standards, but they were particularly underweight. Table 11 shows the absorption and excretion of calcium by the two groups of children, and Table 12 the average figures for nitrogen, magnesium and phosphorus. The amount of calcium in the diet of the control, low-calcium group (A) was less than it had been at the other orphanage, and the average quantity of bread eaten was almost exactly the same (600 g. per day). This is probably one reason why they absorbed less calcium than the children in the other home.

The children in the second group (B), whose diets were exactly the same except for the amount of calcium in them, absorbed three times and retained four times as much calcium as those in the control group, in spite of the fact that they had been receiving the extra calcium for the previous four months. The children who were getting more calcium also absorbed and retained more magnesium. If active formation of bone was taking place in these children, as indicated by the high retentions of calcium and phosphorus, an increased retention of magnesium was only to be expected since magnesium is also an integral part of bone salt. The addition of calcium to the bread depressed

TABLE 11

The absorption and excretion of calcium by children eating bread with and without added calcium carbonate

(Average results for 7 days)

Subject	Intake (mg./day)	Excretion (mg./day)			Absorption		Balance (mg./day)
		Urine	Faeces	Total	(mg./day)	(as per cent of intake)	
Group A	Bread containing *no* added calcium						
Else ..	669	123	407	530	262	39·2	+139
Inge ..	737	30	454	484	283	38·4	+253
Christel ..	729	30	624	654	105	14·4	+ 75
Wolfgang ..	784	103	676	779	108	13·8	+ 5
Herbert ..	804	91	693	784	111	13·8	+ 20
Adolf ..	791	109	660	769	131	16·6	+ 22
Average ..	752	81	586	667	166	22·1	+ 85
Group B	Bread containing added calcium						
Sigrid ..	1,987	101	1,479	1,580	508	25·6	+407
Margot ..	2,200	193	1,786	1,979	414	18·8	+221
Marlies ..	2,083	140	1,657	1,797	426	20·4	+286
Harald ..	2,879	70	2,300	2,370	579	20·1	+509
Horst ..	2,886	136	2,467	2,603	419	14·5	+283
Lothar ..	2,850	131	2,371	2,502	479	16·8	+348
Average ..	2,481	129	2,010	2,139	471	19·0	+342

TABLE 12

The effect of adding calcium carbonate to the diet on the absorption and excretion of nitrogen, magnesium and phosphorus

(Average results for six children for 7 days)

Group	Intake	Excretion			Absorption	Absorption (as per cent of intake)	Balance
		Urine	Faeces	Total			
Nitrogen (g./day)							
A (Low Ca)	12·11	8·07	2·47	10·54	9·64	79·5	+1·57
B (High Ca)	11·98	7·51	2·59	10·10	9·39	78·2	+1·88
Magnesium (mg./day)							
A (Low Ca)	880	130	690	820	190	22·0	+60
B (High Ca)	930	170	630	800	300	32·2	+130
Phosphorus (mg./day)							
A (Low Ca)	2,510	1,000	1,280	2,280	1,230	49·0	+230
B (High Ca)	2,460	750	1,390	2,140	1,070	43·7	+320

the absorption of phosphorus slightly, but an ample sufficiency was still absorbed and the high-calcium group retained more phosphorus than the others. The ratios of the amounts of calcium to phosphorus retained were 0·37:1 and 1·07:1 for the low- and high-calcium groups respectively. For the children in the other orphanage it had been 0·58:1. Macy's healthy children, living on a diet containing little or no phytic acid, retained equal amounts of calcium and phosphorus, as did ten pre-school children studied by Daniels, Hutton, Knott, Everson and Wright (1934). The addition of calcium to the German children's diets, therefore, enabled them to retain calcium and phosphorus in the same ratio as healthy children eating diets containing little or no phytic acid. It also enabled them to retain more than three times as much calcium in proportion to nitrogen as the children who were not having the extra calcium in their diets, and their retention ratio $\frac{Ca}{N} \times 100$ was 18·3.

The children having the larger amounts of calcium in their diets excreted more calcium in their urines. This is in accordance with the observation of McCance and Widdowson (1942b) that the amount of calcium in the urine of adults depended partly upon the amount absorbed and that it varied directly with it. They concluded that changes in the urinary excretions of calcium may be used as an index of changes in the amount of calcium absorbed. It is difficult to understand why the amount of calcium in the urine of the two children studied by Hoff-Jørgensen *et al.* (1946) was quite unaffected by the amount of phytate in their diets, although the quantity of calcium absorbed was very different.

DISCUSSION

From a consideration of the present results and the results of other workers for the amounts of calcium absorbed and retained by individuals of various ages, in various states of calcium nutrition, at various levels of calcium and phosphorus intake, the following points seem clear:

1. Raising the calcium intake facilitates its absorption.
2. Raising the intake of phosphorus, and particularly of phytic acid phosphorus, depresses the absorption of calcium.
3. If the calcium and the phytic acid phosphorus intakes are increased together, so that the proportion of the one to the other remains the same, then more calcium will be absorbed. This is possibly because the absolute amount of calcium in solution in the intestine will have been increased. Conversely, a reduction in the intake of both calcium and phosphorus will result in a smaller calcium absorption.
4. An adult who has been accustomed to a high-calcium diet, and who has been absorbing enough calcium to maintain himself in calcium equilibrium on this diet, would absorb less calcium if his calcium intake were reduced or his phytic acid intake increased, and if the diet were sufficiently poor in calcium or rich in phytic acid he would probably be in negative calcium balance. If he continued to eat this diet he might, after some time, come into calcium equilibrium again, but his bones would have lost some of their calcium in the process.
5. A child who has been absorbing sufficient calcium to maintain himself in positive balance on a high-calcium diet would likewise not absorb so much calcium if his calcium intake were reduced or his phytic acid intake increased. If this diet had produced a negative calcium balance he might, after some time, start to retain calcium again, but his bones would contain less calcium than they would have done had he continued to eat his original high-calcium low-phytic acid diet.

6. If such a child or adult, who has become "adapted" to a low-calcium high-phytic acid diet, then returned to his original high-calcium low-phytic acid diet, he would absorb and retain far more calcium than if he had remained on this diet the whole time. This fact proves that his body must have become short of calcium and really, in itself, contradicts Walker *et al.*'s (1948) assertion that "the consumption of such a diet (rich in phytate phosphorus) over long periods has no deleterious effect on calcium metabolism".

7. The amount of phytate hydrolysed in the intestine to inorganic phosphate depends partly on the amount of calcium in the diet, and varies inversely with it (Cruickshank, Duckworth, Kosterlitz and Warnock, 1945). According to Mellanby (1949) it would not matter if it was hydrolysed or not if the body contained no vitamin D, for in puppies it is only in the presence of this vitamin that phytate has a greater anti-calcifying action than phosphate. Apart from vitamin D, it is possible that the hydrolysis of phytic acid in the intestine may depend upon the type of diet which the person has been accustomed to eating, and that "adaptation" is an increasing ability to hydrolyse phytic acid in the intestine while the intakes of calcium and phytic acid remain the same. If this proves to be true, then the hydrolysis must occur sufficiently high up in the intestine for the calcium to be absorbed. It must presumably be brought about by an alteration in the intestinal flora, possibly giving rise to some change in the reaction of the intestine. McCance and Widdowson (1942a) were not able to demonstate any such change during their experiments, but there was no evidence that any of their subjects had become "adapted" over this admittedly short period of time.

SUMMARY

1. The absorption and excretion of calcium, magnesium and phosphorus have been studied in four groups of persons in Germany in 1947 and 1948. The nitrogen metabolism of three of these groups has also been investigated. The diets of all groups contained large amounts of brown bread.

2. Six out of seven undernourished civilian men were in negative balance for calcium, magnesium and phosphorus.

3. Five repatriated prisoners of war from Russia ate diets providing them with 7,000 Calories a day, about 3,000 of which came from brown bread. Their nitrogen intakes were 30 g. a day and they retained 12 g. From these figures it has been calculated that rather more than half their gain in weight was due to muscle and rather less than half to fat.

4. The diets of these men contained 1·7 g. of calcium a day, and four of them were able to absorb enough calcium to maintain themselves in positive calcium balance, in spite of the large amounts of brown bread they were eating. All five men were in positive balance as regards magnesium and phosphorus.

5. Five boys aged 9–13 years were able to absorb and retain 0·4 g. of calcium a day from their German diets, which provided 0·9 g. of calcium daily.

6. A group of six children who had received diets containing 2·5 g. of calcium a day for four months absorbed three times and retained four times as much calcium as another group of 6 children of similar age and sex, living at the same orphanage, who had been having 0·75 g. of calcium a day. Apart from the calcium, the diets of the two groups were exactly similar in all respects.

7. Some of the factors controlling the absorption and excretion of calcium are discussed.

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XXVII. THE RESPONSE TO UNLIMITED FOOD

by E. M. Widdowson

After the Unit had been working in Wuppertal for four months and the characteristics of the undernourished individual had been fairly well defined, it was felt that the effects of giving a group of such persons an adequate diet might well repay investigation. Such studies have been made before, but never under quite the same conditions and with the facilities which we had at our disposal.

The liberation of the concentration camps in Europe provided one opportunity for making such studies, and several workers have taken advantage of this (Lipscomb, 1945; Lamy, Lamotte and Lamotte-Barillon, 1946; Murray, 1947; Beattie and Herbert, 1947b; Hottinger, Gsell, Uehlinger, Salzmann and Labhart, 1948). These workers suffered from a number of handicaps, however—the desperate plight of their patients, the severe overcrowding and the concomitant disease—and it was often not possible to make all the tests that they would have liked.

Keys, Taylor, Mickelsen, Henschel and Brozek (1946) studied the effects of a diet providing 2,020–4,228 Calories a day for 12 weeks on 32 men who had voluntarily submitted themselves to a period of 6 months of undernutrition. They made most careful studies of the men at the beginning and end of the period of refeeding, but it seems more than likely from Murray's observations and from the results of the present investigation that these men would have eaten much more food and recovered more rapidly had they been given the opportunity of doing so.

THE SUBJECTS OF THE PRESENT INVESTIGATION

General Notes

There were 20 subjects, all men, and their ages ranged from 26 to 80 years. Old as well as young were included for it was thought that they might react differently to unlimited food. Sixteen of the men had previously been admitted to the hospital as in-patients and had formed the subjects of some of the investigations described elsewhere. Four of the older ones had never been admitted before. Some details about the men are given below, and Table 1 gives a summary of their ages and also their degree of undernutrition, as measured by the presence or absence of oedema (*McCance and Widdowson*, p. 1) and their weight as compared with the Hassing-Schall standards. Some of them had been grossly overweight before, and these men had lost a great deal more weight than this Table suggests. Kurt, for example, said he weighed 103 kg. before the war. He should have weighed 69 kg. His actual weight at the beginning of this experiment was 59 kg., which included much oedema fluid. August previously weighed 100 kg. His correct weight for height and age was 80 kg. When admitted to hospital at the beginning of this investigation he weighed 58 kg.

Four of the men were prisoners of war who had been released from Russia during the previous weeks. Their diet there was said to have been 500–600 g. of bread and 1·5–2 litres of soup a day. Since they had been home they had been having "normal consumer" rations with the addition of their supplements for hunger oedema, which provided them with a total of about 1,900 Calories a day. They probably had more than this, for returned prisoners always tended to have preferential treatment within their families. However that may be, they all had

TABLE 1

Description of subjects

Name	Age (years)	Percentage below standard weight for height and age	Oedema grading
Günther	26	0	2
Reinhold	27	16	1
Willi	30	20	2
Hans	44	29	0
Albert	44	17	3
Adolph	52	6	0
Max	53	18	2
Otto	54	16	3
Franz	55	15	2
Emil	55	19	3
Karl	55	18	1
Friedrich	57	23	1
Kurt	58	14	5
August	61	28	3
Oscar	61	22	3
Wilhelm	64	14	2
Paul*	67	13	4
Arthur	76	8	2
Ewald	80	21	3
Ludwig	80	11	4

*Excluded from the investigation a short time after it began.

gained 2–3 kg. in weight during the month they had been home, between the time they were first seen and the beginning of this investigation.

Eleven of the men were in employment up to the time the experiment began. Two were of working age but were on the sick list on account of undernutrition, and three were old-age pensioners. Those who were working were earning 95–190 RM a month, with the exception of Kurt, who was earning 330 RM. The pensioners received 57–130 RM a month, and the repatriated prisoners had no source of income. Sixteen of the 20 were married men, but the three oldest were widowers. Of the thirteen married men whose wives were still living, seven had no other dependants, and six had one to five more persons dependent on them.

In selecting subjects for this experiment an effort was made to exclude men who might be suffering from something more than simple undernutrition, but it was difficult to exclude every other abnormality. Three of the 20 men originally chosen were replaced before the investigation began, one because of a duodenal ulcer, and the others because they had put on so much weight since they were first seen that they could no longer be considered undernourished. One of those finally selected, Paul, was found to have a gastric carcinoma a short time after the experiment began, and it was therefore necessary to reduce the number of subjects to 19. In spite of the fact that he was up to his standard weight at the beginning of the investigation, Günther was included because he still had oedema.

Personal Data

Günther (B 104) had returned from Russia four weeks previously and had then been admitted to hospital in poor condition. He was the youngest of the

party, unmarried, and lived with an aunt. He was tall and broad in proportion, and was already up to his standard weight before the refeeding began. Unreliable and self-seeking, he was disliked by the other men, who regarded him as lazy and gluttonous. He spent more time than any of the others lying on his bed during the day. When the experiment was ended he disappeared and did not return for any of the follow-up clinics.

Reinhold (B 26) had been an epileptic for over ten years, and had been sterilized in 1936. He had worked in a dental appliance factory throughout the war, but had recently been discharged because of his epilepsy. He was mentally subnormal, and had a poor general health record. He lived with his parents, and was obviously more of a liability to them than an asset. His father, who was tall and gaunt, was 27 per cent below his standard weight and had slight oedema. Since his first admission on July 12 1946, Reinhold had taken part in a number of investigations, and he had always proved co-operative. He had been having extra rations for hunger oedema for the preceding nine months.

Willi (B 112) had returned from a Russian camp four weeks before, and had then been admitted to hospital for neurological investigation because of the astonishing briskness of his tendon reflexes. He was at that time acutely miserable and worried that he might not recover his normal health and strength. At the beginning of this experiment he was slightly more cheerful, but had not put on any weight. He had boils and a disfiguring facial pyoderma, which cleared up rapidly with sulphonamide treatment. He was unmarried and lived with his mother. He was intelligent and became the acknowledged jester of the party. He was responsible for keeping the records of the body weights throughout the experiment.

Hans (B 107) had come back from Russia five weeks before and had then entered hospital for a neurological examination. He was unmarried and lived with his mother and sister. At the beginning of this experiment he was extremely thin, and although he had already put on 4 kg., he was still 29 per cent below his standard weight. He more nearly resembled the popular concept of the starved inmates of a concentration camp than any other of our subjects. He was very unhappy and concerned about his health. He sweated profusely, especially at night. He was very particular about personal matters, and considered himself superior to the others. He always brought his own knife and fork carefully wrapped in a clean cloth to the meal table. He was one of those who were entrusted with keeping the dietary records. He had scabies, but this yielded at once to treatment with benzoyl benzoate.

Albert (B 76) was a metal worker, married, with no children, and had been admitted to hospital for a short time six weeks before. He was rather dull mentally, moved and spoke slowly, and was rarely seen to smile. He had a gross kyphosis. He obtained "moderately heavy worker" rations (*McCance and Widdowson*, p. 1), and had also been getting extra rations for hunger oedema for the preceding six weeks.

Adolph (B 109) had been a prisoner of war in Russia until six weeks before this investigation began, and he had not yet started work. He had spent the previous five months in the prison-camp hospital, suffering from undernutrition and malaria, and shortly before joining the party he had a mild recurrence of malaria. Some of the tests made on him during the preliminary week may have been influenced by this. He was handsome and looked much more intelligent than he was. He claimed to be a gardener by profession, and was married but had no children.

Max (B 83) was officially employed as a night watchman in a clothing store, but he was able to sleep the greater part of the night and supplemented his income by delivering newspapers during the day. He lived with his wife and two daughters and was a devout Catholic. He had a bad hare lip and always seemed very miserable. He was an epileptic, but had managed to avoid sterilization. He was admitted to hospital six weeks before this experiment began with gross oedema of the legs and face, and ascites, which did not improve with rest in bed. After his discharge he had received extra rations for hunger oedema, and at the beginning of this experiment his oedema was very much reduced, and his weight was correspondingly lower. During the second week he had a mild epileptic fit of the grand mal type.

Otto (B 100) was a driver on the "Schwebebahn", the electric overhead railway which runs from one end of Wuppertal to the other. He obtained the rations allowed to "moderately heavy workers" and had been having supplementary rations for four weeks on account of his oedema. He was married, and lived with his wife and son. He was quiet, pleasant and hardworking, obviously conscientious, but not very imaginative. He was always neatly dressed and careful of his appearance.

Franz (B 92) was a swimming bath attendant, and attributed the oedema of his legs to the fact that he was constantly getting wet. He had had "normal consumer" rations, with the supplement for hunger oedema for the preceding four weeks. He and his wife lived alone. He was always full of complaints about minor ailments such as pains in the back and legs, and itching. There was perhaps some justification for some of these complaints, since X-ray examination revealed considerable bony fusion in the lower part of his spine.

Emil (B 77) was a metal worker and, when working, had "heavy worker" rations. For the past 3½ months, however, he had been off sick, and during that time had had "normal consumer" rations with the extra allowance for hunger oedema. He lived with his wife, son aged 18, and daughter aged 11. He had been admitted to hospital six weeks before with extensive oedema, and he looked thin and ill. By the beginning of this experiment he looked somewhat better, but his weight was less.

Karl (B 42) was employed at one of the biggest "Schwebebahn" stations, where his job was to marshal the crowds waiting for the trains. He had "normal consumer" rations, and he had received a supplement for hunger oedema since he was first admitted to hospital ten weeks previously. He became the self-appointed leader of the men, and was their spokesman when occasion arose. He and his wife lived alone, and when asked about his previous weight, he was fond of saying that before the war he and his wife together weighed more than 200 kg. !

Friedrich (B 72) had previously been in business, but had lost his job in November 1945 for political reasons. He had been out of work for some time, and had employed himself cultivating his own allotment, but shortly before this experiment started he had begun to work at tree-felling, and for this he received "very heavy worker" rations. He had had, in addition, extra rations for hunger oedema since the time he had first been admitted to hospital, eight weeks earlier. He lived alone with his wife. He was above the average of the men in intelligence, and was one of the three responsible for keeping the dietary records.

Kurt (X 19) was employed as a book-keeper, and earned twice as much as most of the other men. He had, however, to support in addition to his wife two grown-up daughters, a son-in-law and a grandchild. He was conscientious and

meticulous, and besides helping to keep the dietary records, he had his typewriter in the ward, and spent all his spare time copying lists and making calculations. He had gross oedema, which worried him considerably. He had had "normal consumer" rations, and for six weeks a supplement for hunger oedema.

August (B 126) lived with his wife and daughter and worked as a dyer in a textile factory. This was considered to be light work, but he had to stand most of the day. He had not previously been admitted to hospital and he had been getting only "normal consumer" rations with no supplements. He was tall and very thin, and looked grey and ill.

Oscar (B 87) was lame in his left leg, probably from an attack of infantile paralysis in childhood. He was the only skilled craftsman of the party, being employed as a bookbinder. He had to stand at his work. He had had "normal consumer" rations, and extra rations on account of hunger oedema for eight weeks.

Wilhelm (B 37) was employed as a metal worker and received "moderately heavy worker" rations. He had first been admitted to hospital three months previously and had been having extra rations for hunger oedema since that time. He lived with his wife, daughter and grandchild.

Arthur (B 123) was 76 years old, but in spite of this he worked seven hours a day in a factory, and he continued to work for five hours a day throughout the experiment. He received "heavy worker" rations and had also had the supplement for hunger oedema for the previous six weeks. However, his home circumstances were rather unhappy, and there was, in fact, some doubt whether he was allowed to eat his own rations or whether some part was held back by his daughter-in-law with whom he lived. He was therefore particularly pleased to be asked to take part in this experiment.

Ewald (B 120) was 80 years old, a widower, and lived alone. He had no one to care for him, and had to buy his own food and prepare his own meals. When he was visited in his home with the invitation to join the experimental party, he said that he had nothing but one red cabbage in his kitchen to last him for the next few days. He probably, however, had sources of food which he did not disclose. He had been receiving extra rations for hunger oedema for six weeks.

Ludwig (B 124) was another 80-year-old widower living alone; his wife had died the previous year. He had an allotment which he kept in very good order, and this must have provided considerable additions to his official rations. For four weeks he had also been getting a supplement for his oedema. He had a great sense of humour, but found the communal life rather trying. He obviously enjoyed working (see p. 323).

GENERAL ORGANIZATION OF THE EXPERIMENT

The men lived in the Städtisches Krankenhaus, Barmen. The three wards which had been set aside for us were used as bedrooms, and we were allowed the use of a large room as dining room. Another smaller room served as a sitting room during the evenings. The main experiment lasted for nine weeks, from September 30 to November 30, 1946. For the first week the men were given only the ordinary hospital diet, and during this time all the preliminary tests, clinical, biochemical and radiological, were made. Unlimited Calories were then provided for eight weeks. This food came from three sources: firstly from the ordinary hospital diet, which the men continued to receive; secondly from margarine, sugar, cheese, potatoes, and bread, which were obtained through the

German food office; and thirdly from tinned meat and fish, dried milk and cocoa, which came from British supplies.

Arrangements were made with the local labour office that all of the men who wished should work in the hospital grounds clearing up rubble and levelling a large bank (Plates LV and LVI). It was explained to the men that manual work in the open air was part of their treatment, and that if they worked they would have better appetites and be able to eat more food, but no compulsion was put on any of them to work. They were paid for their work at half the normal rate since they were receiving sick benefit as well, and a record was kept of the number of hours each man worked each day. The work was classified as light, medium or hard, and each man was encouraged to do the hardest work of which he was physically capable.

The men had breakfast at 8 a.m. They worked from 9 to 12, with a short break for a cup of cocoa at 10·30. At 12 they had their midday meal. They rested on their beds until 3 p.m., then worked again until 5 p.m. They had a cup of "Ersatz" coffee when they came in, and the evening meal was served at 6 p.m. Card-playing was the chief spare-time occupation. Some of the men read a little, and several spent a great deal of time keeping the records of the experiment, particularly the dietary records.

Wednesday and Saturday afternoons and all day Sunday were treated as holidays. This gave the men an opportunity to visit their families or to have their families to visit them. Those who lived near often went home after the evening meal, but they were expected to be in again by 9 p.m. Two of the men were allowed to spend one or two nights at home during the course of the experiment, one on the occasion of his silver wedding, and the other because he was having some repairs done to his house and he had to help his wife move the furniture during the evening in readiness for the workmen next day. Max continued his work as a night watchman throughout the experiment by leaving after his evening meal and returning in time for breakfast. Arthur also continued to go to his work in the mornings and afternoons, but came to the hospital for all his meals.

Some tests were made daily, some once or twice a week, and others only at the beginning and end of the experiment. After the main experiment ended, the men who took part in it visited us periodically for the next two years. At first they came once a month, and later every two or three months until their 12th and last visit on October 30, 1948. They were weighed on each occasion, and, after 15 minutes' rest on a bed, their blood pressures and pulse rates were taken and a note was made of the presence or absence of oedema. They were asked whether they were able to sleep well, whether they suffered from giddiness or parasthesiae, and whether they were very hungry or not. Inquiries were also made about the work they had been doing since their last visit, the rations they received, and how many times they had to get up in the night to empty their bladders. In May 1947, and February and October 1948, venous blood samples were taken for the estimation of serum protein and cholinesterase, and haemoglobin and haematocrit levels were determined on the last occasion.

The Diets

The hospital ration supplied about 1,900 Calories a day. The daily allocation of cheese, tinned meat, fish, dried milk and cocoa provided another 1,500 Calories, and bread, potatoes, sugar, and margarine were always available in unlimited quantities, so that Calories were virtually unrestricted.

The hospital allocation of 210 g. bread with 16 g. butter and 35 g. jam was eaten for breakfast, and this was supplemented by 100 g. cheese and unlimited further supplies of bread, margarine and sugar. "Ersatz" coffee was drunk with 100 c.c. of fresh milk, which was the hospital ration for the day. The sugar was used to sweeten the coffee, and the men were allowed to sprinkle it over their bread or, if they wished, to eat it alone with a spoon. The 10·30 cocoa was made from full-cream dried milk, cocoa and sugar. The midday meal consisted of soup and vegetables supplied by the hospital, supplemented by 100 g. of tinned meat (chopped pork or corned beef) and potatoes. Their "Ersatz" coffee at 5 p.m. was made with dried milk, and unlimited sugar was available. The allocation of dried milk, together with the hospital ration of fresh milk, provided the equivalent of 1,000 c.c. of whole milk a day. The evening meal consisted of soup, supplied by the hospital, followed by 100 g. tinned meat or fish with as much potato as desired, and finally bread, spread with butter and a little sausage or cheese, which was part of the hospital ration. Thus, every man was able to eat bread, potatoes, fat and sugar according to his taste and appetite, and had a "ration" of 1,000 c.c. of milk, 200 g. tinned meat or fish and 100 g. of cheese each day. The men were not allowed to take any of the food home and care was taken to see that they did not. The meals were always supervised by one of us and all the uneaten food had to be left in the dining room. The men who were responsible for weighing the food were very vigilant, and the others stood little chance of removing uneaten food from the table.

All the food eaten by 12 of the men was weighed every day for the first six weeks. The food of each of the other men was weighed for one of these weeks. Three spring balances were available, and the men were divided into three groups. One out of each group undertook to be responsible for the weighing of all the food eaten by himself and three others, and sometimes by a fifth man as well. These three men took a great interest in what they were doing, and kept the records faithfully and conscientiously. They considered the weighing their responsibility and very much resented anyone else assisting with it. All those whose food was being weighed had individual pots for margarine and sugar, into which 50 g. or 100 g. portions were weighed as desired. Each day was treated separately, and any margarine or sugar that was left at the end of the day was weighed back and a fresh start was made the next morning. The quantities of bread, potatoes, margarine and sugar eaten by each man were calculated for each separate day, and also the daily average for each week of the investigation. The Calories provided by the total diet, and the amounts of protein, fat and carbohydrate in it were also calculated. Figures provided by the Food and Agriculture Division of the Control Commission, and the Tables of McCance and Widdowson (1946a) were used for this purpose. Some foods were specially analysed.

RESULTS

Food Intakes and Calories

The first breakfast. The men first had access to unlimited food on Monday, October 7, 1946. They had all been short of food for the past 18 months—some for much longer—and the amounts they ate deserve some comment. All the men had more than 2,000 Calories, four of them more than 3,000 at this one meal. Willi, aged 30, had 114 g. of margarine, 200 g. of sugar, 80 g. of cheese and 525 g. of bread, and his breakfast provided him with 3,954 Calories. Günther, aged 26, had the second highest Calorie intake (3,282), which was made up by 89 g. of

margarine, 125 g. of sugar, 165 g. of cheese and 700 g. of bread. Both these men were repatriated Russian prisoners. One of the 80-year-old men, Ewald, came next on the list with 3,170 Calories. He ate 79 g. of margarine, 100 g. of sugar, 85 g. of cheese and 535 g. of bread. The average amount of margarine eaten was 73 g., of sugar 92 g., of cheese 108 g. and of bread 488 g. This first breakfast provided an average of 83 g. protein, 111 g. fat and 370 g. carbohydrate, and 2,756 Calories.

Breakfast was always a slow meal because of the quantity of bread it contained (McCance and Widdowson, 1946b), and the men usually took about an hour to eat it. There was very little diminution in the amount of food eaten at breakfast as time went on, and it was always the most popular meal of the day.

The Calorie value of the diets. The average Calorie intake of the 12 men whose food was weighed for the first six weeks of the experiment was just under 6,000 a day. Murray (1947), who studied the recovery of 1,000 persons from Sandbostel concentration camp, found that his patients were not satisfied on the Army "Compo" ration which provided about 3,600 Calories a day, and it was necessary to supplement this diet with potatoes and dairy produce until the total Calorie intake was about 8,000 a day before the subjects' appetites were appeased. This enormous diet seems to have been well tolerated and it was continued for three weeks. When, in 1948, repatriated prisoners of war from Russia were given access to unlimited amounts of food, largely in the form of bread, they were able to eat enough to provide them with 7,000 Calories a day (*Widdowson and Thrussell*, p. 296). The present group of men probably started in a better state of nutrition than Murray's, for their weight averaged 59·3 kg. as against 54·2 kg. for Murray's subjects, and it is possible that, had our men been more severely undernourished, they would have eaten more food still. Be that as it may, it seems quite clear that the subjects investigated by Keys *et al.* (1946) were probably not given as much food as they would have been able to eat, and their rate of recovery may have been limited by this.

The diets of the 12 men contained a little more protein, fat and carbohydrate during the first experimental week than during any subsequent one, and the average Calorie intakes were highest then (see Table 2), but the differences were

TABLE 2

Average daily Calorie intakes and amounts of protein, fat and carbohydrate in the diets during the preliminary week and six experimental weeks

	Calories/ day	Protein (g./day)	Fat (g./day)	Carbohydrate (g./day)
Preliminary week ..	1,860	60	38	329
Week 1 ..	6,108	204	221	853
„ 2 ..	5,998	197	216	850
„ 3 ..	5,960	202	207	852
„ 4 ..	5,832	198	206	825
„ 5 ..	5,910	195	214	834
„ 6 ..	5,875	194	205	843

not statistically significant. Five of the 12 men had fewer Calories during the first week than during the sixth. Four of the men had their highest Calorie intake on the first day of the experiment, two on some other day during the first week.

Günther was the only one who reached 8,000 Calories on any one day, and he achieved this on four separate occasions. On two of these days his Calorie intake exceeded 8,800. Six other men had more than 7,000 Calories on several days in the six weeks during which their food was weighed. Five of the men maintained a Calorie intake sufficient to give them an overall average of over 6,100 a day. The remaining seven all had between 5,000 and 6,000 Calories a day.

Bread, potatoes, fat and sugar. Table 3 shows the average amounts of bread, potatoes, margarine and sugar eaten daily by the 12 men whose food was weighed consistently during the six successive weeks of the experiment. The

TABLE 3

Average daily amounts of the unrestricted foods eaten by 12 *men during the preliminary week and* 6 *of the experimental weeks*

	Bread (g./day)	Potatoes (g./day)	Margarine (g./day)	Sugar (g./day)	Soup (g./day)
Preliminary week	320	200	24	0	1,343
Week 1 ..	570	751	104	142	1,606
„ 2 ..	552	767	103	166	1,773
„ 3 ..	625	673	97	142	1,532
„ 4 ..	586	673	99	144	1,594
„ 5 ..	588	646	102	165	1,505
„ 6 ..	600	626	100	155	1,522

quantities supplied during the preliminary week are also shown. The figures for bread, margarine and sugar show small fluctuations, but there was neither significantly more nor significantly less eaten at the end than at the beginning. The figures for potatoes, on the other hand, did show a decline after the first two weeks of unlimited diet, and the difference between the average for the second and sixth weeks was statistically significant ($t = 2{\cdot}6$, $P = 0{\cdot}01$–$0{\cdot}02$).

The amounts of soup consumed are also shown here. Soup was often left over in other wards, particularly the women's wards, and this was always sent to our men, so that each could usually have as much as he desired. The men seemed to be able and willing to consume big helpings of soup in addition to the large quantities of other foods which they ate. The average was highest during the second experimental week. Ten of the 12 men had more soup during that week than in any other.

The records for the individual men showed some wide deviations from the averages. Günther, for example, ate much less towards the end than he did at the beginning, his average Calorie intakes falling steadily from 7,321 to 5,729 a day during the six weeks of the investigation. This was brought about by a decrease in the consumption of all foods but particularly of margarine and sugar. Albert, on the other hand, ate more and more with each succeeding week of the experiment, his average daily Calorie intake rising steadily from 5,876 during the first experimental week to 6,405 during the sixth. Hans also ate increasing amounts of all foods except potatoes as the experiment proceeded.

The effect of age on food intake. In order to compare the appetites of the older and younger men, the subjects were divided into three age groups, and their average intakes have been calculated. For this purpose all 19 men have been included, whether their food was weighed for one week or for six. In the former

case the daily average over one week was taken, in the latter the daily average over six weeks. Of the 12 men whose food was weighed for the whole six weeks, 4 were in the youngest age group, 5 in the middle and 3 in the oldest. Table 4 shows the average daily Calorie intakes and the amounts of protein, fat and carbohydrate in the diets of the men in each of the three age groups; it also shows the average quantities of the unrestricted foods which the men ate each day.

TABLE 4

The effect of age on food intake

	26–44 yr. (5 men)	52–58 yr. (8 men)	61–80 yr. (6 men)
Calories/day	6,038	5,946	5,617
Protein (g./day) ..	198	199	190
Fat (g./day)	215	212	199
Carbohydrate (g./day)	851	839	791
Margarine (g./day)	109	101	91
Sugar (g./day) ..	165	147	138
Bread (g./day) ..	585	610	561
Potatoes (g./day) ..	708	652	606
Soup (g./day) ..	1,472	1,578	1,528

The older men clearly did not eat quite so much food as the younger ones. They ate nearly as much bread, but less potato, margarine and sugar, and their Calorie intakes were lower. The old men had good appetites, nevertheless, and all 6 men in the 60–80-year-old age group had higher Calorie intakes than Reinhold, aged 27, Adolph, aged 52, or Karl, aged 55. It is true that the youngest man in the investigation, Günther, had the highest Calorie intake, but the second youngest had the second lowest.

TABLE 5

Percentage of the total Calories derived from different foods

Foodstuff	Percentage of total Calories provided by food		
	Average	Maximum	Minimum
Bread	25·3	30·1	22·8
Margarine and butter	13·4	18·3	10·8
Milk	10·2	11·8	8·9
Sugar	9·9	12·6	6·9
Soup	9·8	12·8	4·5
Meat	9·7	11·2	8·5
Cheese	6·1	7·6	4·9
Fish	2·4	3·3	1·5

Distribution of the Calories. Bread provided all the men with more Calories than any other food (Table 5). The percentage of the total Calories obtained from bread varied from 22·8 to 30·1 with an average of 25·3, taking all 19 men together. The result was almost identical if only the 12 men whose food was weighed for six weeks were considered. Margarine was the second most important

source of Calories, followed by milk, sugar, soup and meat, all of which provided about 10 per cent of the Calories in the diet. When the diets are considered in terms of proximate principles, 13·8 per cent of the Calories came from protein, 33·4 per cent from fat and 52·8 per cent from carbohydrate.

Work and Morale

The morale of most of the men was excellent throughout the whole of the nine weeks of the experiment. The only difficulty arose over the payment for the work done in the hospital grounds. There was unfortunately a misunderstanding at first, and the men were told that they would receive the full rate of pay for the work they were doing. It was decided subsequently by the local labour office that this was not feasible since the men were also in receipt of sickness benefit, besides their free board and lodging in hospital, which included this ample diet. Some of the men resented this, and refused to work unless they received what they had originally been promised. The whole position, and how the misunderstanding had arisen, was then explained to them, and they were given the option of leaving at once if they were still not satisfied. None of them did so. Table 6

TABLE 6

Percentage of the possible working hours which 15 *of the men worked*

Subject	Age	Percentage of total possible hours worked
Günther	26	35
Reinhold	27	83
Hans	44	36
Albert	44	82
Adolph	52	40
Max	53	49
Otto	54	85
Franz	55	74
Emil	55	68
Karl	55	78
Friedrich	57	62
August	61	83
Oscar	61	76
Wilhelm	64	69
Ludwig	80	93

shows the percentage of the possible number of working hours which 15 of the nen spent on this work during the first six weeks of the experiment. Four of the nen were omitted from this list, Arthur, because he was at his usual work, Willi, because he spent most of his time searching for a job which he might take up when he left the hospital, Kurt, because he had so much oedema that he was kept in bed part of the time, and Ewald, because of his rheumatism. The emaining 15 were physically able to work, although one or two of the epatriated prisoners did not feel strong enough to do so during the first week. It is nteresting to note that the oldest man, Ludwig, worked the greatest number of ours, and the youngest, Günther, the least. It was Günther who incited the men o refuse to work unless they were paid more money.

The men became much brighter and happier as the experiment proceeded. At first they were apathetic, miserable and inclined to grumble and were showing at that time, therefore, psychological effects which were so characteristic of the German civilian population in 1946. As time went on the atmosphere changed, partly, no doubt, because they got to know each other better. There was more and more good-natured chaffing and joking; they frequently expressed pleasure at the good treatment they were receiving, and their faces, previously haggard and unhappy, now began to look cheerful and contented (Plates LVII to LXII). At the end of the whole experiment they had a party, and there is no doubt that the jovial spirit which pervaded it would not have been possible nine weeks earlier.

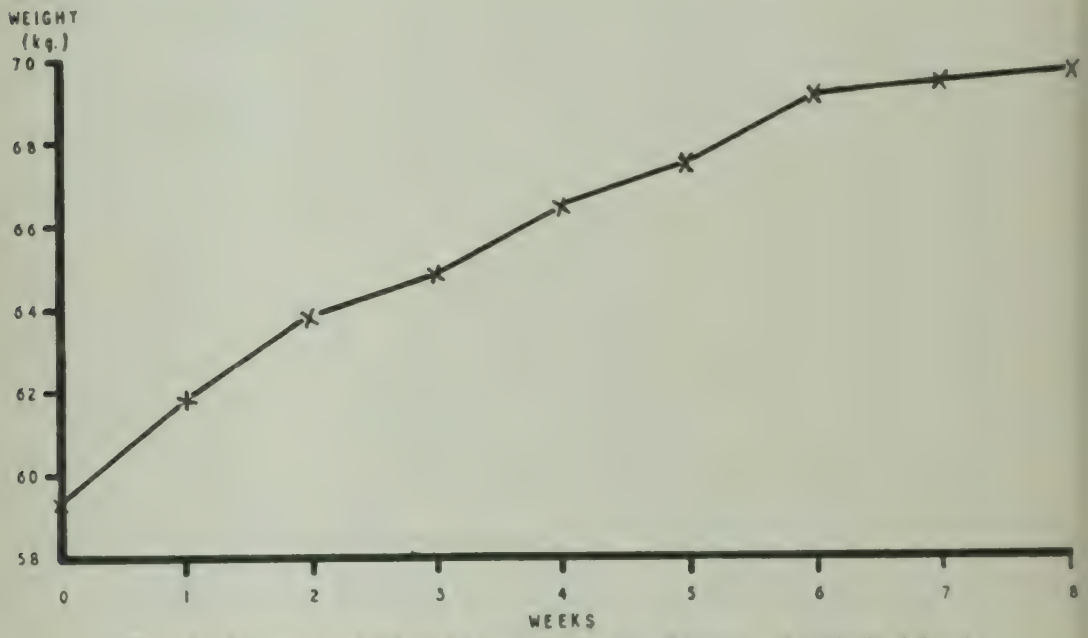

FIG. 1. Average weight of 19 men during the 8 weeks of unlimited food.

Body Weights and Measurements

All weights were taken under standard conditions, before breakfast, naked, and with the bladder emptied. The men were weighed twice weekly as a general rule, but during the preliminary week and the final week of the experiment the weights were taken more frequently. Fig. 1 shows the average weights of the 19 men throughout the course of the experiment and Fig. 2 the average increments in weight during the first six weeks of the unrestricted diet.

The average weight of the men at the beginning of the investigation was 59·3 kg., which was 17·3 per cent below what it should have been according to the Hassing-Schall standards. At the end it averaged 69·6 kg., or only 2 per cent less than the average "standard" figure for this group of men. The average gain was, therefore, just over 10 kg. About one-quarter of this was put on during the first week and one-fifth of it during the second (Fig. 2). Murray found that among the liberated inmates of Sandbostel concentration camp who were eating a diet providing 8,000 Calories a day, 58 per cent of the total gain in weight took place during the first 7 of the 23 days of his investigation.

The weights of individual men were from 0 to 29 per cent below the standard for height and age at the beginning of the experiment (Table 1). At the end of the eight weeks seven were up to their standard weight or above. August was

still 14 per cent underweight and Hans 12 per cent, but these were by far the thinnest men at the beginning, when they were 28 per cent and 29 per cent underweight respectively. The men gained between 4·4 kg. (Adolph) and 14·8 kg. (Otto), and the increments varied from 6·6 to 24 per cent of their weights at the beginning of the experiment. The bouts of diarrhoea (p. 329) always led to a small loss of weight, which was soon regained, the loss being probably due largely to a loss of body fluid.

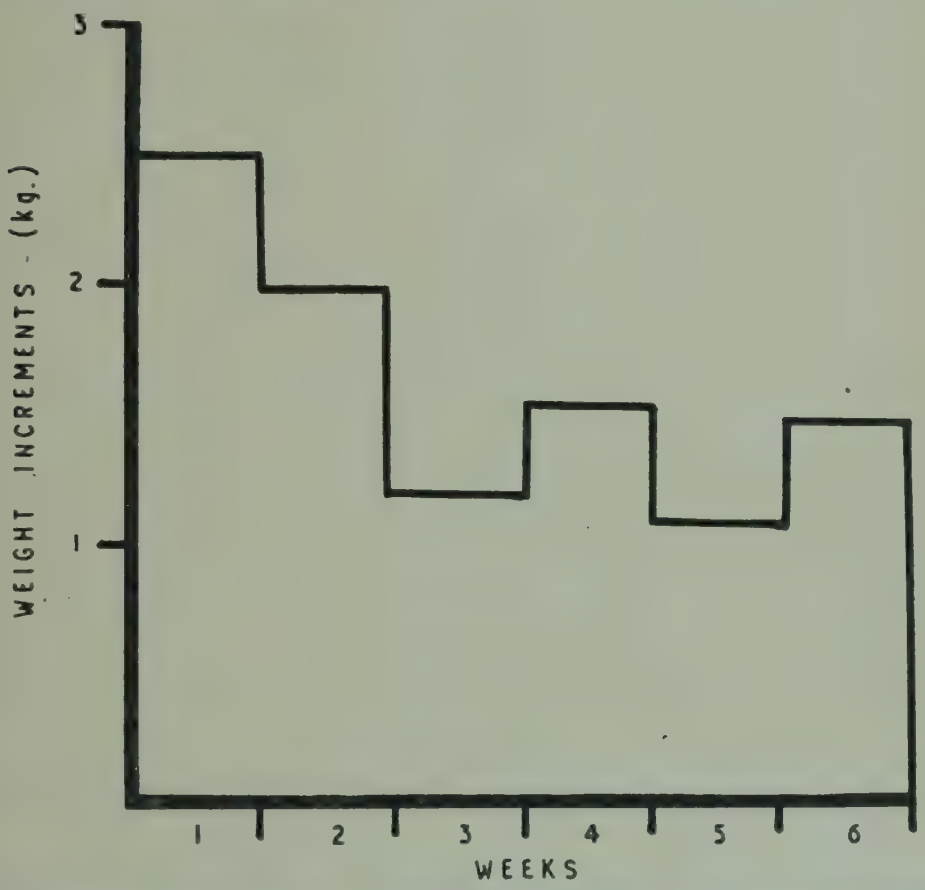

FIG. 2. Average weekly increments in weight during the first 6 weeks of unrestricted diet.

The effect of age on weight increase. The men were divided into three age groups as on p. 322, and the effect of the diet on their average body weights is shown in Table 7. The middle group was slightly lighter than the youngest group at the beginning of the experiment, and the oldest men were lighter still. The older men happened to be shorter than the men in the younger age groups, and when their weights were calculated as a percentage of their standard weights, all three groups were about the same.

The two younger groups gained the same amount of weight. The oldest group put on 1 kg. less, but since they weighed less at the beginning, their percentage increase in weight was not much lower than that of the younger age groups. The way in which these older men reacted to the diet was most instructive. They were able to eat nearly as much food as the younger ones (Table 4, p. 322), and they gained nearly as much weight. The two youngest men, Günther and Reinhold, aged 26 and 27, put on 10·1 and 8·6 kg. respectively; the two oldest, Ewald and Ludwig, both 80 years old, gained 10·3 and 9·5 kg. over the same period of time, which was no mean performance.

TABLE 7

The effect of age on weight increase

	26–44 yr. (5 men)	52–58 yr. (8 men)	61–80 yr. (6 men)
Average weight at beginning (kg.)	61·3	60·0	56·7
Weight at beginning as percentage of standard for height and age	84	84	83
Average increase in weight (kg.) ..	10·8	10·7	9·5
Increase as percentage of original weight ..	17·6	17·8	16·8
Final weight as percentage of standard for height and age ..	99	98	97

Intakes of Calories and increments of weight. The daily Calorie requirement of the "average man" is generally considered to be of the order of 3,000 a day, and on this he does not gain or lose weight. Our men took approximately 3,000 Calories a day more than this over the eight weeks of the experiment, and this enabled them to put on 10 kg. of body weight, or 178 g. a day. If all these "additional" 3,000 Calories had been laid down as body fat the weight increment should have been over 300 g. a day; if it had been laid down as muscle the increase would have been very much more. In actual fact, the weight increase was probably due to increments of both fat and muscle (*Widdowson and McCance*, p. 165; *Widdowson and Thrussell*, p. 296). It is quite clear that on these very generous diets a considerable proportion of the "surplus" food was immediately metabolized.

Weights over the next two years. When the men left the hospital and went home, they returned to a diet which, even with their extra rations for hunger oedema, only provided about one-third as many Calories as they had been receiving for the previous eight weeks. The winter of 1946–7 was a severe one, fuel was short, and it is little wonder that both physically and psychologically they went downhill. They seemed most miserable in February 1947, and there were many complaints of coldness and hunger. The average body weight fell steeply until the beginning of March (Fig. 3), then more slowly until the end of June, but it was still 3 kg. above what it had been before the experiment started. With the warmer weather and improvements in the rations and in the supplies of vegetables, the weights began to rise again until, in October 1948, the men had regained an average of 4 kg., and the final level was 3 kg. below what it had been at the end of the experimental period.

Body measurements. During the preliminary and final weeks of this investigation measurements were made of the circumference of the neck, right upper arm, forearm, thigh and calf, and of the supracristal and trochanteric circumferences. The measurements were made as carefully as possible with a good tape measure, with the subject standing completely undressed. The time of day was the same on each occasion and was four hours after the previous meal.

The points for measurement were obtained as follows: *Neck*: The head was thrown very slightly back so that the skin of the neck was just beginning to

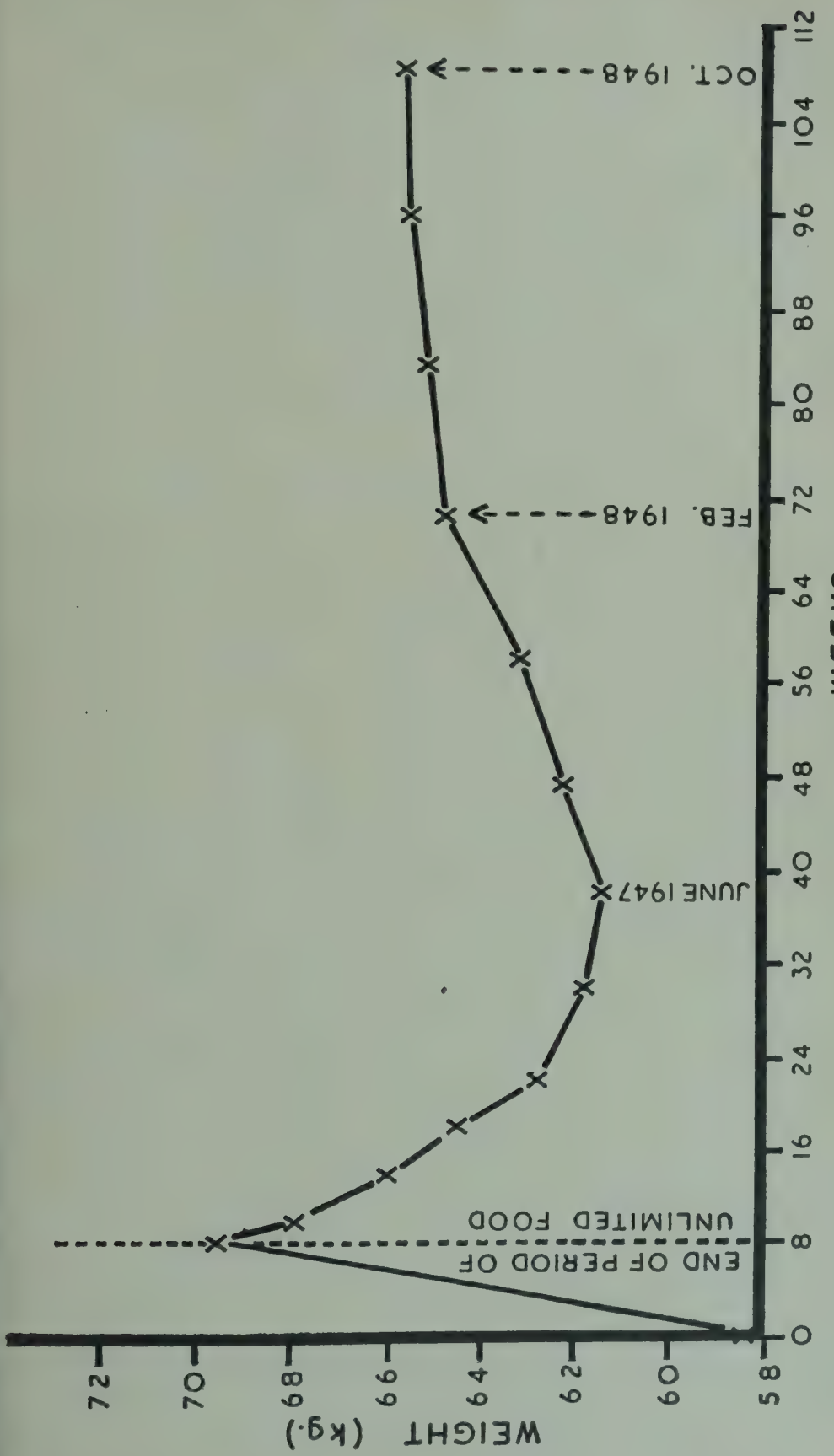

FIG. 3. Average body weight during and after the experiment.

stretch. The circumference was then taken at the base of the neck. *Upper arm*: The distance from the anterior tip of the acromium process to the external condyle of the humerus was measured, and at the mid-point the circumference of the upper arm was taken. *Forearm*: The greatest circumference was taken, at right angles to a line pictured as running longitudinally through the centre of the forearm. The arm was always measured as it hung loosely by the side. *Supracristal and trochanteric circumferences* were measured at the level of the highest point of the pelvis and at the maximum protuberance of the great trochanters, respectively. *Thigh*: The distance from the anterior superior spine of the iliac crest to the joint line between the femur and tibia on the lateral aspect was measured, and at the mid-point the circumference was taken. *Calf*: The largest circumference in a horizontal plane was taken.

TABLE 8

Percentage increase in body measurements

Circumference measured	Average percentage increase	Maximum	Minimum	Standard deviation
Neck	4·5	11·1	1·6	5·17
Upper arm ..	15·2	23·6	5·0	5·42
Forearm ..	7·3	12·5	0·0	3·33
Thigh	12·1	21·0	4·2	4·86
Calf	6·8	11·8	1·8	3·14
Supracristal .. diameter ..	7·4	16·7	1·4	3·58
Trochanteric diameter ..	7·2	11·7	2·0	2·84

Table 8 gives the percentage increases which took place in these various measurements. The circumference of the upper arm showed the greatest increase in 15 out of the 19 men, and the largest average increase. In five of the men this measurement increased by more than 20 per cent. This improvement had been very noticeable, for when the venepunctures had been made at the beginning of the investigation it was easy for the assistant to encircle the whole of the upper arm with her hand in order to apply slight constriction, but at the end this was no longer possible.

The circumference of the thigh showed the second largest increase, and for two of the men, Hans and Willi, this was their biggest change. Keys *et al.* (1946) found that the changes in the circumference of the thighs, as of the other limbs, of the men taking part in their experimental study of starvation and rehabilitation followed very closely the changes in body weight. In their subjects the circumference of the thigh was still well below the original circumference after twelve weeks on a diet providing 3,600 Calories a day. What our men's thighs measured before they became undernourished is not known, but after eight weeks of a diet providing 6,000 Calories a day the measurement had increased by 12·1 per cent as compared with 10·4 per cent found by Keys *et al.* in their subjects.

Keys *et al.* found that the abdominal girth recovered more rapidly than any other measurement. In the present investigation the supracristal circumference showed a smaller percentage increase than the circumference of the upper arm or thigh, but it is impossible to say how nearly it had returned to its size in health.

Body measurements were made of several other groups of men who were being given improved diets of various sorts during the course of the next two years, and among these was a group of repatriated prisoners of war from Russia. *Widdowson and McCance* (p. 165), *Hutchinson, McCance and Widdowson* (p. 216), *McCance, Dean and Barrett* (p. 135) and *Widdowson and Thrussell* (p. 296) described how these men gained weight, and appeared to become excessively fat soon after their return to Germany. During the first eight weeks after 6 of these prisoners had returned, while they were leading lives of inactivity and spending most of their time lying on their beds, they put on an average of 13·3 kg. in weight (*Hutchinson et al.*, p. 216). The average neck, upper arm and forearm circumferences increased by very much the same percentages as those of the 19 men described above, but the circumference of their thighs and calves showed average increases of 19·8 and 13·6 per cent respectively, and their supracristal and trochanteric diameters increased by 13·9 and 10·6 per cent, which is considerably more than those of the present series.

Clinical Observations

General health. The health of the men was on the whole good. In turn, nine of them had diarrhoea which lasted from one to four days. This was not traceable to any particular infection, nor did it seem to be related in any definite way to the diet, for it affected one man in the first experimental week, one in the second, three in the third, one in the fourth, two in the fifth and one in the sixth. The attacks were all very much alike. They began at night and the bowels were opened three or four times within the next few hours; the stools were fluid but not very watery, and there was no blood and very little mucus. The diarrhoea subsided over the next 24 hours, but the man felt unwell, with headache and weakness, and his temperature was raised to about 99°–99·5°F. (37·2°–37·5°C.). His tongue was dry and coated, and he had some abdominal tenderness which was rather more marked in the upper quadrants. There was no vomiting and little loss of appetite.

If patients with diarrhoea are excluded, the average number of stools per day increased from 0·65 during the preliminary period to 1·75 during the experimental weeks. The average number did not vary from one experimental week to another.

One of the epileptics, Max, had a fit during the second experimental week, and Ewald complained of rheumatism and seldom went out of doors. There were no other ailments worthy of mention.

All the 19 men complained of continuous hunger before the experiment started, but only two of them at the end. Of these, Max, the night watchman, only felt hungry when he was making his rounds during the night; the other, Ewald, was an old man and was not a reliable witness. Probably none of them really felt hungry at this time. They did not seem to feel particularly hungry for two months after they left the hospital, but in January 1947 all of them complained of perpetual hunger, and they said that the hunger was as bad as it had been before they had the plentiful diet. This hunger continued throughout 1947 and for the first few months of 1948, but by May of that year, complaints were fewer and the men admitted that they were getting more to eat. By July they all agreed that their hunger was no more than a normal appetite for meals.

Eight men professed to feel unduly thirsty on their ordinary home diets in

September 1946, and five of them continued to be so after eight weeks of unrestricted feeding.

Eight of the men complained of sleeping badly before the experiment started, but only two at the end. Of these, one was Ewald, who was suffering from earache at the time he was questioned and this kept him awake. The other was Wilhelm, aged 64, who said the other men in the ward disturbed him. Both Ewald and Wilhelm said they slept well before the experiment started.

All 19 of the men considered that they were excessively tired before the beginning of the experiment. At the end, eight said they still got tired more easily than they should, but the other eleven no longer complained of tiredness.

Giddiness was found to be a very common manifestation among persons suffering from chronic undernutrition (*Davis*, p. 147). Fourteen of the men complained of giddiness at the beginning, but only four at the end of the experiment. Of these, two were the epileptics, Reinhold and Max, and the other two, August and Ewald, were aged 61 and 80 respectively.

Nine of the men professed to be troubled by parasthesiae of the fingers or toes before the experiment started, and of these, two had lost the sensation by the end. Six men still complained of giddiness and five of parasthesiae on their last visit in October 1948.

At the beginning of the investigation none of the 19 men admitted that he had any interest in sexual matters. This is a very common finding in undernutrition, and was noted by Keys *et al.* (1946) in their experimental study. At the end of the experiment five of the men said their sexual feelings had returned to normal. Four of them were married and were aged 52, 54, 55 and 57; two of these said that their wives, unlike themselves, were still not interested in sexual intercourse. The fifth was unmarried and aged 26.

Of the 12 married men under 70 who were questioned about their sexual feelings in October 1948, nine said that these had now returned to normal, and the improvement in each case dated from the summer of 1948. Three still said there had not been any change.

This information cannot be regarded as entirely satisfactory, but it suggests that the general improvement in physical and mental health included a return towards normal in the sexual life of the men.

Nocturia. The nocturia which has been noted by so many investigators of undernutrition in the past was one of the chief complaints of the patients who attended the out-patient clinic (*McCance and Widdowson*, p. 1). The 19 men taking part in this investigation suffered in the same way, and it was decided to keep a record of the number of times each night that each of them got up to empty his bladder. During the preliminary week, before the dietary régime was started, all of the men got up at least twice and ten of them 5 times or more every night. As the investigation proceeded there was a slight reduction in this nightly parade, and by the end of the eight weeks only three of them got up 5 times or more. The average fell from 4·7 at the beginning to 3·4 at the end.

Each time the men came to the hospital for "follow-up" study during the next two years they were asked how many times they had to get up at night. Fig. 4 shows their averaged answers. There was clearly an increase in the amount of nocturia after they went home again and they continued to be disturbed more than 4 times a night on the average until February 1948. Then there was a decrease, and by the following July the average had fallen to 2·6, but even at this time all the men had to get up once or more.

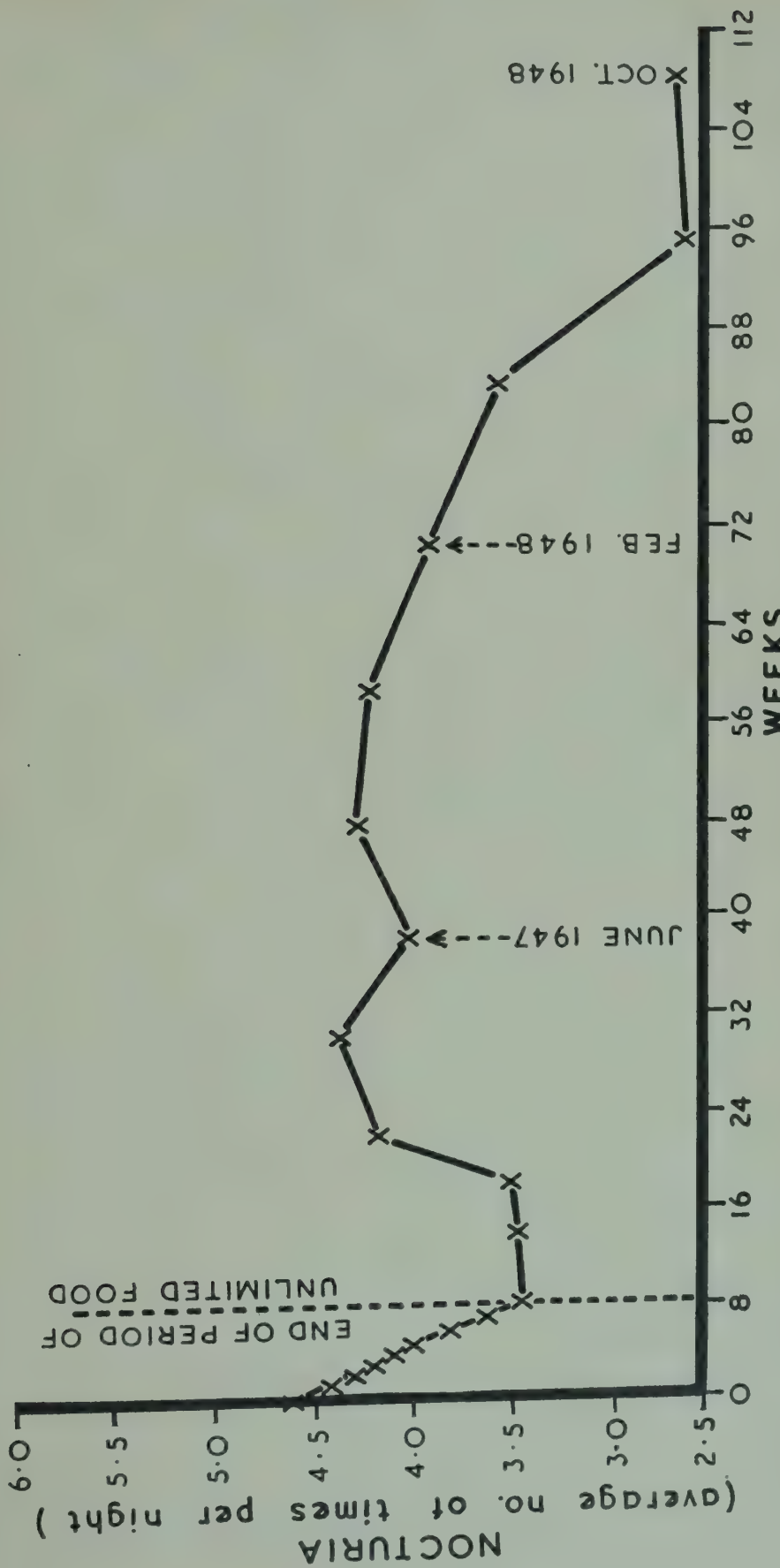

FIG. 4. Nocturia during and after the experiment.

It will be described how 20 other men, who had been admitted to hospital during 1946 and the beginning of 1947, attended for re-examination in January 1949. These men were questioned about their nocturia on both occasions. In 1946–7 they got up 5 times a night on the average; in January 1949 the mean figure was 1·7.

Davis (p. 147) has suggested that the nocturia may have been related to the sleeplessness which was part of the psychological syndrome seen in the German population. It undoubtedly also had some connexion with the large volumes of salt soup that were eaten and many patients said that they purposely took no soup in the evening in order to avoid getting up so many times in the night. A more fundamental cause was probably the increased volume of extracellular fluids (p. 342).

Blood pressure. Low blood pressures have been reported by various workers as being the rule in undernutrition (Keys, Brozek, Henschel, Mickelsen and Taylor, 1945; Brull, 1945; Lups and Francke, 1947; Bok, 1949; see also *McCance and Widdowson*, p. 1) and the blood pressures of the men admitted for this investigation were no exception. At the end of the experiment, eight of the men were found to have had an increase in their systolic and diastolic pressures, seven to have had a decrease, and four to have had no change. Three of the four repatriated prisoners showed a rise of blood pressure; the initial figure for the fourth is uncertain because he was recovering from malaria when the first measurement was made. Two of the three oldest men, Arthur and Ewald, showed a considerable decrease, for their pressures fell from 200/110 to 145/70 and 200/95 to 140/60 mm. Hg, respectively; the blood pressure of the third, Ludwig, did not change. The results for these three men have been excluded from the averages given in Table 9. There was no consistent trend, either in the systolic or diastolic pressures, and there was certainly no change of any statistical significance after eight weeks of a Calorie intake which averaged 6,000 a day.

TABLE 9

Blood pressure

(Average of 16 men)

	Lying		Standing	
	Systolic B.P. (mm. Hg)	Diastolic B.P. (mm. Hg)	Systolic B.P. (mm. Hg)	Diastolic B.P. (mm. Hg)
Beginning	109	65	121	75
End ..	114	64	122	76

During the next four months, when the men were at home eating their ordinary rations, there seemed to be a tendency for the systolic and diastolic pressures to rise, and by the beginning of March 1947 the averaged value was 120/72 mm. Hg. The rise in systolic pressure was probably significant ($t = 2{\cdot}50$, $P = 0{\cdot}02$–$0{\cdot}05$). The pressures did not rise any more over the next 18 months, which suggests either that these men had always had somewhat low blood pressures or that, as a result of the period of undernutrition, some change in the vascular system had occurred which had caused a reduction in blood pressure from which no complete recovery could be made.

Some support to the latter suggestion is given by the work of Keys *et al.* (1946) and of Lups and Francke (1947). Both of these groups of workers were able to

measure the blood pressures of their subjects before the period of starvation began. Keys *et al.* found the systolic arterial blood pressures decreased by 12 mm. Hg as a result of 24 weeks on a diet providing 1,700–1,800 Calories a day. After 12 weeks of rehabilitation, when the diet provided 3,600 Calories a day, recovery was only 81 per cent, and the blood pressures of the groups of men whose diets had provided 2,400–2,800 Calories a day only recovered by 26 per cent after the same length of time. Lups and Francke reported the blood pressures of several hundred patients who visited their clinic in Utrecht in 1942–4 before the period of starvation started, in April 1945 when starvation was at its worst and 80 per cent of the patients had lost at least 20 per cent of their body weight, and again in September 1945 when nearly everybody had gained weight as a result of the improved rations. They found a fall in systolic and diastolic pressures in all age groups in April 1945, and on the average, a further small decrease in September, in spite of the gain in weight.

A further opportunity arose of studying whether the general improvements in Germany in 1947 and 1948 had occasioned any change in blood pressure of the population. Twenty men, who had been admitted to hospital as suffering from undernutrition during 1946 and the early part of 1947, were invited to attend for re-examination in January 1949. The ages of these men ranged from 23 to 65 years, with an average of 48 years, and their blood pressures, taken in bed, had averaged 110/67 mm. Hg in 1946–7. The men's general health had improved by 1949, and their average weight had increased by 10 kg. They had also lost their oedema almost completely. Their blood pressure in January 1949, taken after 15 minutes on a couch, averaged 122/72 mm. Hg, which represented a small but definite increase (systolic, $t = 2{\cdot}36$, $P = 0{\cdot}02$–$0{\cdot}05$). The conditions were not exactly the same on the two occasions, and it is possible that this would have accounted for the results.

Pulse rate. A fall in pulse rate is one of the characteristic signs of undernutrition, and it has been observed repeatedly (*McCance and Widdowson*, p. 1). The pulse rates of 15 of our men were taken before they rose from bed on three successive mornings. The other four were not measured, one because he was a night watchman and arrived at the hospital only in time for breakfast, another because he had malaria during the preliminary week and two because they were not in hospital for the whole of the preliminary week. The results for the 15 men showed that the unrestricted diet caused a rise in all the pulse rates except one, which did not change. The increase ranged from 9 to 19 and averaged 12 beats per minute. The mean value at the beginning was 55 and at the end 67 beats per minute, and the increase was statistically significant ($t = 7{\cdot}6$, $P = <0{\cdot}01$). Two years later the average for the same 15 men was 65 beats per minute.

The effect of exercise on the pulse rates of these men at the beginning and end of the experiment is described by *Glaser*, (p. 280).

The group of men who were recalled for examination in January 1949 (see above) may also be considered in this connexion, although their pulse rates were taken during the morning after 15 minutes on a couch, and not before they got up for breakfast. Five of them had recently returned from Russia when they were first admitted to hospital, and they showed the characteristically high pulse rate of such persons, with an average value of 79 beats per minute. In January 1949 the average had dropped to 68, which was exactly the same as the final average for the other 15 men, whose initial level had been 62 beats per minute. Thus, the returned prisoners of war, whose high pulse rates might be considered as part of their effort syndrome (*Davis*, p. 147), had, as might have

been expected, reacted differently from the patients who had become undernourished in Wuppertal.

Basal metabolic rate. It is well known that a fall in basal metabolic rate accompanies undernutrition. It is also known that the "reduction in metabolism which results from starvation is proportionately greater than the reduction in body mass" (Duncan, 1947). In other words, the basal metabolic rate falls more than would be expected from the loss of body substance. This phenomenon, although it may be the result of the undernutrition, has the effect of conserving body tissue which would otherwise be lost more extensively.

The Knipping apparatus at the Barmen hospital measured the consumption of oxygen and the output of carbon dioxide, and the results have been calculated per square metre of body surface (Du Bois, 1936). It will be seen from Table 10

TABLE 10

Basal metabolic rate

(Average of 19 men)

	O_2 consumption (c.c./sq. m./min.)	CO_2 output (c.c./sq. m./min.)	Respiratory quotient
Beginning	115	90	0·78
End ..	123	102	0·83

that there was a small rise in oxygen consumption (from 115 to 123 c.c. per sq. m. per minute) during the experiment, and a somewhat greater rise (from 90 to 102 c.c. per sq. m. per minute) in the output of carbon dioxide. The former is probably significant ($t = 2{\cdot}48$, $P = 0{\cdot}02$–$0{\cdot}05$) and the latter certainly is so ($t = 3{\cdot}58$, $P = <0{\cdot}01$). It will be realized that these changes involved an increase in the respiratory quotient, and this rise is also statistically significant ($t = 5{\cdot}1$, $P = <0{\cdot}01$). If the present results are compared with the Sage (Aub-Du Bois) standards for basal metabolism (Du Bois, 1936), assuming the heat produced during the combustion of 1 litre of oxygen to be 4·8 Calories, the average basal metabolism was 88 per cent of the standard at the beginning, and 94 per cent at the end.

It will be noted that the figures for these men before they had access to unlimited food were somewhat higher than those for the 70 men described by (*McCance and Widdowson*, p. 1). This agrees with the clinical impressions made at the time, and with the fact, already discussed, that some of our subjects had started to improve before the experiment began. The basal metabolic rates of 13 of the experimental subjects had been determined when they were admitted to hospital one to three months earlier. At that time their oxygen consumption had averaged 104 c.c. per sq. m. per minute. At the beginning of October the average value for the same 13 men was 113 c.c. per sq. m. per minute, and at the end of the eight weeks of generous diet it was 125 c.c. per sq. m. per minute. Beattie and Herbert (1947a,b) studied the basal oxygen consumption of 11 Dutch and 11 German subjects, all of whom were emaciated after prolonged undernourishment. The measurements were made shortly after the patients were first admitted to hospital, and on several subsequent occasions after they had been partaking of experimental diets for some weeks. The authors related the Calorie intakes per kg. body weight to basal oxygen consumption, also expressed per kg., and they found that when the intake was approximately 35 Calories per

kg. per day the rate of heat production was normal at the beginning, but in later tests the oxygen uptake was not related to the Calorie intake, and in fact the German subjects showed a fall in oxygen uptake as the Calorie intake increased. Beattie and Herbert suggest that this may have been because they were burning relatively more carbohydrate than fat on the later occasions, and because protein was being conserved. These results are hardly comparable with the present ones, for our men were taking 100 Calories per kg. per day.

Body temperature. Rectal temperatures were taken before the subjects rose from bed on three successive mornings at the beginning and end of the experiment. Low temperatures were not found and there was no change as a result of the extra food.

Electrocardiography. Simonson, Henschel and Keys (1948) and Bok (1949) have noted that in starvation there was a reduction in voltage of the electrocardiogram, showing particularly in the QRS complex, and that, as a result of good feeding, the voltage returned to normal.

At the beginning and end of the experimental period E.C.G. records were made, using the usual three leads. Unfortunately the apparatus could not be perfectly standardized because it was old and the technicians could not guarantee its accuracy. It is, however, certain that the errors, if any, were small and not systematic, because the voltages and deflections of a large number of normal E.C.G. records taken over the same period of time were carefully examined, and they did not change.

Evidence of changes similar to those observed by Simonson *et al.* was found in the men at Barmen. In 15 of the 19 the voltage rose as estimated by the maximum height of the QRS complex. The 5 men whose voltage increased most gained no more weight than the average; their oedema did not alter appreciably; their extracellular fluid volumes did not fall more than the average. It seems, therefore, that the increase in voltage was probably an effect of alterations in the heart itself rather than an effect caused by changes in the volume of blood or other body fluids.

The radiological appearance of the heart at the beginning and end of the investigation is described by *Berridge* (p. 260).

Gastric acidity and the response to alcohol. Fasting gastric juice was withdrawn from all the men at the beginning and end of the investigation. Only three of the samples contained free acid at the beginning and five at the end. The average volume and amount of "total acid" was unchanged. Similar results were obtained from a series of 65 other patients, all men, and most of them between 40 and 70 years old, who were investigated during 1946. Only 6 had any free hydrochloric acid in their fasting juice.

After 300 c.c. of 5 per cent alcohol 4 of the subjects of the dietary investigation secreted free acid during the preliminary period, and 7 of them at the end of the investigation. Again, the average volume and "total acidity" remained the same.

Out of the 65 patients referred to above, 20 responded to a similar dose of alcohol by secreting free acid in their gastric juice.

Radiological observations on the gastro-intestinal tracts of the 19 experimental subjects are discussed by *Berridge* (p. 97).

Strength as measured by dynamometer pull. A hand dynamometer was used and the average of three readings was taken. Measurements were made once a week throughout the experiment. The average reading for all the men was 33 at the beginning and 36 at the end. The increase was probably statistically

significant ($t = 2{\cdot}17$, $P = 0{\cdot}02$–$0{\cdot}05$). These readings were very low, for even the women members of the Unit had no difficulty in "pulling" 40 on this machine, and the men could achieve a reading of 65 quite easily. It is true that the older men reduced the German average a little, for when the men were divided into three age groups as in Table 4, the average value for the youngest group was 34 at the beginning and rose to 40 at the end, while the 6 men over 60 "pulled" 31 at the beginning and 32 at the end. Even so, the performance of the German men must be ranked as very poor. Every effort was made to ensure that they did the best of which they were capable, but it is possible that some of them could have done better had they tried harder.

Serum and Blood Volumes

Keys *et al.* (1946) measured the blood volumes of 16 of their experimental subjects at the different phases of their investigation. By the end of the period of semi-starvation the absolute volume of the plasma had increased by 10 per cent of its original value but, because there was a considerable fall in haematocrit, the blood volume had decreased by 10 per cent. During rehabilitation both plasma and blood volume fell, so that after 12 weeks the plasma volume was 5 per cent and the blood volume 15 per cent below the pre-experimental level. Both were, however, still appreciably above normal, when expressed per kg. of body-weight. Walters, Rossiter and Lehmann (1947) made blood volume determinations on Indian prisoners of war evacuated from Japanese prison camps soon after they were admitted to hospital, and again shortly before discharge, when their body weights had increased by an average of 16 kg. It was found that the absolute volumes of both plasma and blood, which were low at first, increased as a result of the better food, so that these results are in direct contradiction to those of Keys *et al.* The plasma volume expressed as c.c. per kg. of body weight was above normal when the patients were admitted, and decreased during the recovery period. When referred to surface area the plasma volume did not change.

Blood volume determinations were made on all our 19 men during the preliminary week, and again during the last week. The men were up and about on both occasions, and sat on a chair for the test. Evan's Blue (T 1824) was used. After the preliminary sample of blood had been taken, 5 c.c. of a 1 per cent solution of the dye in normal saline was injected intravenously, and six minutes later the second sample of blood was withdrawn. Serial samples of blood were not taken (see Cruickshank and Whitfield, 1945) since the men were being subjected to so many investigations and vein punctures about this time that their number was kept as low as possible. Exactly the same technique was followed on both occasions, so the results are strictly comparable with one another. Determinations were made about three hours after the last meal, and the sera of two of the men were so fatty on the second occasion that it was impossible to make accurate readings, and the results for these two men had to be discarded. Table 11 shows the results on the other 17 men.

The serum volume rose as a result of the unrestricted diet, and the increase in the absolute volume was statistically significant ($t = 3{\cdot}42$, $P = <0{\cdot}01$). Expressed on the basis of surface area (c.c. per sq. m.), however, the serum volume did not change, and it actually fell when referred to the body weight ($t = 3{\cdot}03$, $P = <0{\cdot}01$). The blood volume also rose, from an average of 5,587 to 6,519 c.c., and this increase was also statistically significant ($t = 3{\cdot}75$, $P =$

$<0{\cdot}01$). The rise in blood volume was proportionally greater than the rise in serum volume because there was at the same time an increase in haematocrit Consequently there was a small rise in the blood volume per unit of surface area, and the fall in the blood volume expressed as c.c. per 100 g. body weight was not large enough to be significant ($t = 1{\cdot}37$, $P = 0{\cdot}2$).

These results confirm those of Walters *et al.* (1947), and it is difficult to understand why the findings of Keys *et al.* were so different.

Haematology

Haemoglobin concentration. Most workers have reported a subnormal haemoglobin level in the blood of the undernourished persons they were

TABLE 11

Serum and blood volumes

(Average of 17 men)

	Beginning	End
Serum volume (c.c.)	3,371	3,621
Serum volume (c.c./ sq. m. surface area)	2,000	2,010
Serum volume (c.c./ 100 g. body weight)	5·63	5·23
Blood volume (c.c.)	5,887	6,519
Blood volume (c.c./ sq. m. surface area)	3,490	3,600
Blood volume (c.c./ 100 g. body weight)	9·83	9·41

investigating (Keys *et al.*, 1946; Walters, Rossiter and Lehmann, 1947; Bok, 1949), though Brull (1945) did not find a fall among the population of Liége and he attributes this to the fact that they were eating wholemeal bread.

Haemoglobin determinations were made on venous blood, collected with the minimum of constriction, at the beginning and end of the investigation. Posture was the same on each occasion, the men being up and about for some hours before the blood was collected. The average value for the 19 men was 12·2 g. per 100 c.c. before the experimental diet started and 13·1 g. per 100 c.c. at the end. The rise was statistically significant ($t = 4{\cdot}63$, $P = <0{\cdot}01$). On October 30, 1948, blood was again taken from these men, and the average concentration of haemoglobin was then 14·1 g. per 100 c.c., which was significantly higher than it had been at the end of the period of unrestricted diet ($t = 8{\cdot}12$, $P = <0{\cdot}01$). It is evident that the degree and kind of undernutrition which was found among the civilian population in Wuppertal in 1946 was accompanied by a slight degree of anaemia, and that eight weeks of unlimited food, which included plenty of protein and plenty of iron, were not sufficient to bring the haemoglobin levels to normal. A further rise took place over the next two years, although during this time the body weights were not maintained at the levels they had reached in December 1946.

Total circulating haemoglobin. Since there was a rise in blood volume as a result of the unrestricted diet, and also an increase in the concentration of haemoglobin in it, there was an increase in the total amount of haemoglobin in the circulating blood. At the beginning the average value was 730 g., and at the

end 858 g., and the increase was statistically significant ($t = 4{\cdot}45$, $P = <0{\cdot}01$).

Haematocrit. The average haematocrit at the beginning was 42·0 per cent, and at the end of the experimental period, 44·0 per cent ($t = 2{\cdot}5$, $P = 0{\cdot}02$). There was a further increase during the next two years which paralleled the rise in haemoglobin concentration. In October 1948 the average value for haematocrit was 47·5 per cent, which was significantly higher than the average level after eight weeks of unlimited food two years earlier ($t = 6{\cdot}17$, $P = <0{\cdot}01$).

Differential counts. Two series of differential white cell counts, at the beginning and end of the experiment, were made by the pathologist of the British General Medical Hospital at Iserlohn, and the results are presented in Table 12. It will be seen that there was no important change.

TABLE 12

*Differential white cell counts**

(Average of 19 men)

	Polymorphs	Lymphocytes	Monocytes	Eosinophils
Beginning	62	26	8	2
End ..	58	34	6	0

*200 cells counted and results expressed as percentages.

Serum Chemistry

Proteins. Although a great deal of work has been done on the concentration of serum proteins in undernutrition, and particularly in hunger oedema (*McCance*, p. 21), there is not so much information about the changes that occur when recovery takes place as a result of extra food. Keys *et al.* (1945) found only a very small fall in the total protein concentration in the serum as a result of their low Calorie diet for 24 weeks, and, with improved rations for 12 weeks, a very slight rise (Keys *et al.*, 1946). The albumen/globulin ratio appears to have decreased during the period of rehabilitation. Walters *et al.* (1947) found a low concentration of proteins and a low albumen/globulin ratio in the serum of Indian prisoners of war when they were first admitted to hospital. As a result of better feeding in hospital, the concentration of total protein rose, and the increase was entirely due to a rise in the albumen, so there was at the same time a return of the albumen/globulin ratio towards normal. Beattie, Herbert and Bell (1948), who estimated the total protein concentration in the serum of Dutch and German subjects when they were severely undernourished and again after they had been given a good diet for some weeks, found that, where the level had been low at the beginning, it rose as a result of the better food. When the total proteins were within normal limits, the change was inconsistent in amount and direction.

Table 13 shows the average concentration, on five different occasions, of total protein, albumen and globulin and the albumen globulin ratio in the sera of the men taking part in the investigation now being described. Average values which were obtained for 13 healthy British men are also given. In September 1946 the German subjects had subnormal concentrations of total protein and of albumen, and the difference was in each case significant (total protein, $t = 3{\cdot}07$, $P = <0{\cdot}01$; albumen, $t = 5{\cdot}23$, $P = <0{\cdot}01$). They had, on the other hand, rather more globulin in their serum, but the difference was not significant ($t = 1{\cdot}47$,

$P = 0{\cdot}1$–$0{\cdot}2$). There was a significant rise in the level of total serum protein as a result of the unlimited food ($t = 5{\cdot}63$, $P = <0{\cdot}01$), and this higher level was maintained over the next 15 months. Between February and October 1948 there was a further rise, which was possibly due to the great change for the better which followed the currency reform in Germany.

The increase in total protein concentration during the eight weeks of unlimited food was entirely due to an increase in the globulin fraction. There was no change in the albumen over this time. The rise in serum globulin was statistically significant ($t = 6{\cdot}87$, $P = <0{\cdot}01$), and this resulted in a significant fall in the albumen/globulin ratio ($t = 4{\cdot}63$, $P = <0{\cdot}01$). During the next five months, however, the level of serum albumen rose, while that of the globulin fell, so

TABLE 13

Serum proteins

(Average of 19 men)

	Total protein (g./100 c.c.)	Albumen (g./100 c.c.)	Globulin (g./100 c.c.)	Albumen/ globulin ratio
Beginning ..	6·43	4·14	2·30	1·80
End of 8 weeks on unrestricted food	7·14	4·18	2·96	1·41
After 5 months on German rations (May 3, 1947) ..	7·16	4·61	2·55	1·81
February 7, 1948	7·12	4·49	2·63	1·75
October 30, 1948	7·54	4·90	2·64	1·85
Average for 13 normal men ..	6·96	4·81	2·06	2·35

that the albumen/globulin ratio was restored to its pre-experimental level. The increase in albumen was statistically significant ($t = 5{\cdot}33$, $P = <0{\cdot}01$), as were also the fall in globulin ($t = 3{\cdot}58$, $P = <0{\cdot}01$) and the rise in albumen/globulin ratio ($t = 4{\cdot}45$, $P = <0{\cdot}01$). Over the next nine months there was little change in the level either of albumen or of globulin, but the increase in total protein during 1948 was due more to albumen than to globulin, and there was a slight rise in the albumen/globulin ratio.

In another section of this Report, *Hutchinson et al.* (p. 216) describe an investigation into the effect of a dietary supplement providing 1,860 Calories a day, either as margarine or as protein and fat in the form of skimmed milk, corned beef and cheese, on the activity of the cholinesterase in the serum. The concentration of albumen and globulin in the sera of the two groups of six men taking part in these experiments was determined, as it was also in the sera of ten repatriated prisoners of war from Russia, who were studied during the time they were gaining weight very rapidly (*Widdowson and McCance*, p. 165). The average results for these three series of patients are shown in Table 14. The concentration of total serum protein rose in each case. The albumen/globulin ratio was normal at the beginning for both of the civilian groups, and it fell a little after the six weeks of additional food because the globulin rose more than the albumen, and, in fact, on the diet containing additional protein and fat, the serum albumen was unchanged. Thus, both these groups of men

TABLE 14

Serum proteins of three other groups of undernourished men who were receiving additional rations

		6 civilian men receiving additional fat for 6 weeks*	6 civilian men receiving additional protein and fat for 6 weeks*	10 repatriated prisoners from Russia receiving additional Calories (chiefly as cereals) for 8 weeks†
Total protein	Beginning	5·86	6·34	6·87
	End	6·34	6·53	7·42
Albumen	Beginning	3·89	4·22	4·10
	End	4·15	4·20	4·79
Globulin	Beginning	1·97	2·12	2·76
	End	2·19	2·33	2·63
Albumen/ globulin ratio	Beginning	1·98	1·99	1·49
	End	1·90	1·81	1·82

**Hutchinson et al.* (p. 216).
†*Widdowson and McCance* (p. 165).

showed changes similar to those seen in the 19 men who formed the subjects of the main experiment, but the changes were smaller.

The repatriated prisoners reacted rather differently. Their albumen globulin ratio was low at first, and it rose during the eight weeks of observation because the increase in total protein was entirely due to an increase in albumen. Whether these men reacted differently from all the others because they had a relatively high concentration of serum globulin at the beginning, or because they were at a different stage in the recovery process, or because they ate a different diet, or because they were so inactive, or for some quite different cause, is not known; but the fact that they did react differently makes the results of other workers, who have reported an increase in the albumen fraction only (Walters

TABLE 15

Cholinesterase activity of the serum

	"Pseudo" cholinesterase activity (c.mm. CO_2/c.c./min.)		"True" cholinesterase activity (c.mm. CO_2/c.c./min.)	
	Average	S.D.	Average	S.D.
Beginning ..	47·4	7·65	0·917	0·127
End of 8 weeks on unrestricted food	75·2	13·00	1·020	0·145
After 5 months on German rations (May 3, 1947) ..	55·4	11·49	0·969	0·145
October 30, 1948	67·0	8·28	1·032	0·116

et al., 1947; Weech, 1939), or in the globulin fraction (Keys *et al.*, 1946; Taylor, Mickelsen and Keys, 1949), or in both (van Oven, 1946), fall more into line.

Cholinesterase activity. McCance, Widdowson and Hutchinson (1948) reported a fall in the activity of cholinesterase in the serum during undernutrition and suggested that the average level of activity was a delicate index of the state of nutrition.

The rise in activity of this enzyme in the serum of the 19 men during the course of this investigation has already been described by these authors. Table 15 shows the average values obtained for the activity of "pseudo" and "true" cholinesterase in the serum before the extra food was given, at the end of the eight weeks of unrestricted diet, after a further five months on German rations, and again, in October 1948, when catering in Germany had become much easier. The increase during the time in hospital was statistically significant for both enzymes ("pseudo" $t = 12{\cdot}2$, $P = <0{\cdot}01$; "true" $t = 2{\cdot}63$, $P = 0{\cdot}02$–$0{\cdot}01$). With a return to the German civilian rations there was a fall in the level of the two enzymes, and the decrease in the "pseudo" cholinesterase activity was statistically significant ($t = 6{\cdot}6$, $P = <0{\cdot}01$). The three men who had maintained their increases in body weight after leaving hospital had also maintained their cholinesterase levels better than the rest. By October 1948 the level of this enzyme had risen again ($t = 2{\cdot}70$, $P = 0{\cdot}02$). The significance of these and other findings, and the technique used for the enzyme determinations are discussed fully by *Hutchinson et al.* (see p. 216).

Water Metabolism

Oedema. At the beginning of the investigation all but two of the men had some degree of oedema of the legs. When the oedema was graded as described by *McCance and Widdowson* (p. 1), three were classed as very slight (1), six as definite but not severe (2), five as moderate (3) and one as gross (5). At the end of the eight weeks of unlimited food, seven of the men had lost some of their oedema, but four of them had developed more than before, and the remainder had about the same amount. The frequency distribution of the incidence of the various degrees of oedema, which is shown in Fig. 5, was exactly the same as it had been at the beginning.

The men themselves were disappointed that their oedema had not disappeared with the improvement in their body weights and general physical condition and, for the last few days of the investigation, it was decided to give them less salt in their diets by reducing the amount of soup. By these means the body weights and the oedema were somewhat decreased, but the oedema returned as soon as the men went home, and two weeks later it was exactly the same as it had been before.

The men paid 12 visits to the hospital during the next two years and each man's degree of oedema was recorded. Fig 5 shows the frequency distribution of the various grades of oedema on 4 of these visits. Results can only be given for 17 of the 19 men because one of the old men, Ludwig, died during 1947, and the youngest, Günther, did not attend. In January 1947, six weeks after the period of unrestricted diet came to an end, there was an increase in the amount of oedema, but by the following May it had started to diminish again, and it decreased steadily over the next 18 months until, in October 1948, only 4 of the 17 men who attended the follow-up clinics showed visible pitting oedema of the legs, as compared with 13 of the same group at the end of the experimental period. Of these, Arthur and Ewald were 78 and 82 years old respectively,

Oscar had a lame leg and Kurt had always had more oedema than any of the others.

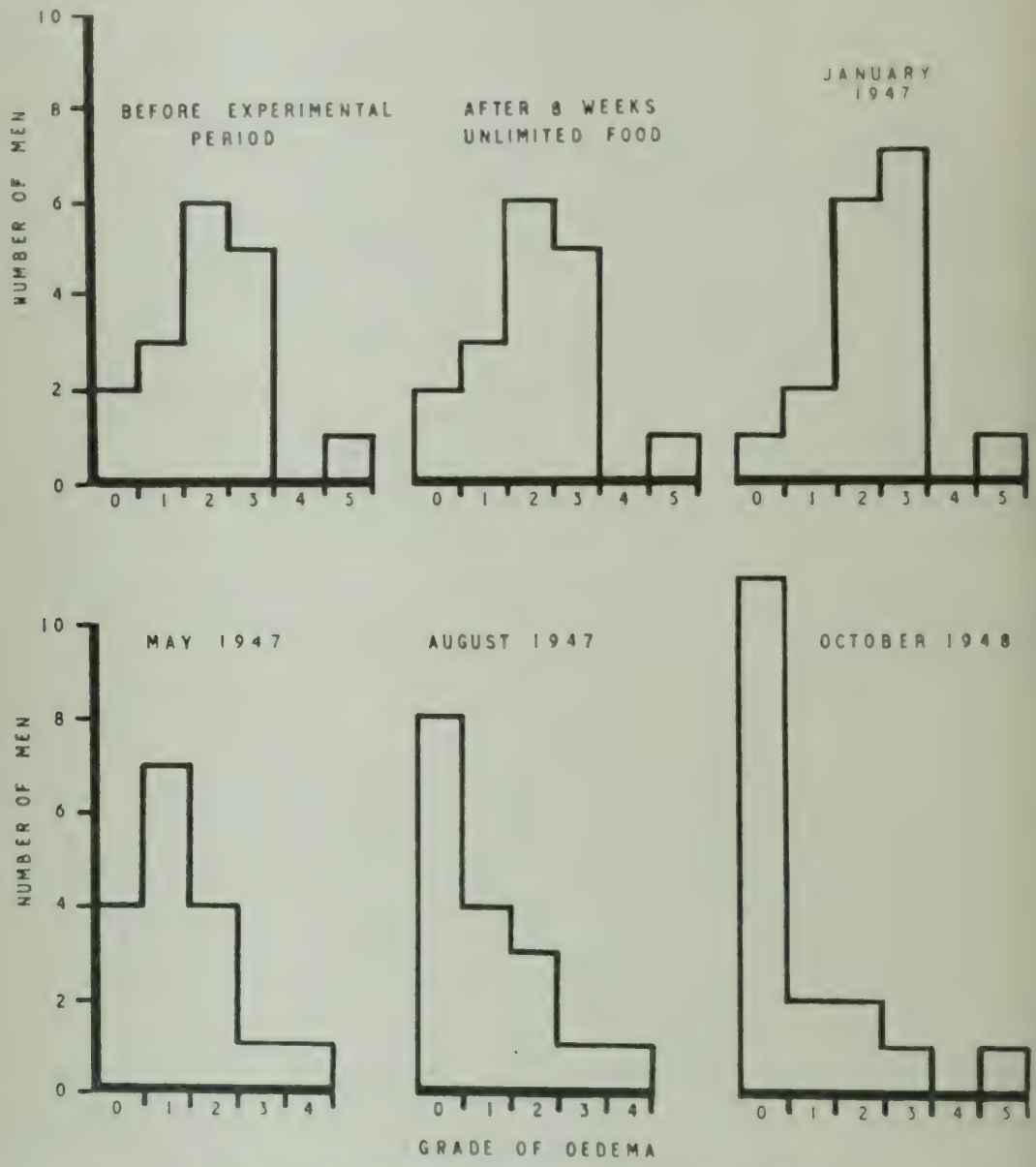

FIG. 5. Frequency distribution of the grades of oedema.

Extracellular fluid volumes. The extracellular fluid volumes of the men were measured at the beginning and end of the experiment as described in the Appendix to this Report (p. 401). The improved diet brought about a decrease in the absolute volume of extracellular fluids, from an average of 22·8 litres to one of 18·1 litres, in spite of the fact that the average body weight had increased by 10 kg. The fall was shown by 18 of the 19 individuals and the difference was significant ($t = 6{\cdot}6$, $P = <0{\cdot}01$). Expressed as a percentage of the body weight, the volume of extracellular fluids decreased from 38·0 to 26·2 per cent following the unrestricted diet ($t = 10{\cdot}0$, $P = <0{\cdot}01$), but even at the end the figure was above the 21–23 per cent, which was obtained by the same technique on healthy members of the Unit (McCance and Widdowson, 1951).

Beattie *et al.* (1948) measured the thiocyanate space of 11 German subjects when they were severely undernourished, and again 8 to 56 days later, after they

had been eating a diet providing a maximum of 2,530 Calories a day. The thiocyanate space amounted to about 34 per cent of the body weights at the beginning, and the changes were in the same direction as those observed in the present investigation but were very much smaller, presumably because the Calorie intakes were so much lower.

There seemed to be little correlation between the volume of extracellular fluids of our subjects and the amount of clinical oedema, either at the beginning or the end of the investigation. Hans, for example, who had no oedema at the outset, and whose extracellular fluids at that time accounted for 38·8 per cent of his body weight, had oedema of the legs which was graded as "2" at the end, in spite of the fact that his extracellular fluids had then decreased by 3 litres and only amounted to 28·8 per cent of his body weight. Adolph at the beginning had 25·1 litres of extracellular fluids and no oedema; at the end he had 15·6 litres of extracellular fluids and grade "2" oedema. This enormous loss of extracellular fluids probably accounted for his small gain in weight (p. 325).

The composition of the urines. The concentration tests were carried out as described by *McCance* (p. 175) and the results are given in Table 16. Similar tests were made on 24 healthy German prisoners of war in England.

TABLE 16

The volume and concentration of the urine after 16 *hours without fluids* (*erect attitude*)

	Average for 19 men		Average for 24 healthy, well-nourished men
	Beginning	End	
Minute volume (c.c.)	0·87	0·82	0·62
Osmotic pressure (m. osmol./l.) ..	835	972	1,034
Chlorides (2 × m. equiv./1.)	460	418	523
Urea (m. mol./1.) ..	227	320	358

The 19 men had significantly higher urine volumes than the controls at the beginning ($t = 8{\cdot}55$, $P = <0{\cdot}01$), and the osmotic pressure and concentration of urea were significantly lower ($t = 4{\cdot}85$, $P = <0{\cdot}01$; $t = 7{\cdot}37$, $P = <0{\cdot}01$, respectively). These are the differences that have been shown to accompany undernutrition, but they may have been magnified in this group by the fact that the average age was appreciably higher than that of the controls. After two months of unrestricted diet the osmotic pressure of the urine was significantly higher than it had been at the beginning ($t = 3{\cdot}55$, $P = <0{\cdot}01$), owing to a rise in the concentration of urea ($t = 5{\cdot}08$, $P = <0{\cdot}01$). Similar changes were brought about by administering sodium chloride and urea to a group of prisoners in Siegburg gaol, and the results may be taken to mean that the kidneys of these men were not under the full influence of post-pituitary hormone even though the men were standing up and had been without fluids for 16 hours. The volume of the urine was still significantly higher than that of the normals after the two months of unrestricted diet ($t = 2{\cdot}28$, $P = <0{\cdot}01$) and the concentrations of sodium chloride and urea were significantly lower ($t = 3{\cdot}88$, $P = <0{\cdot}01$; $t = 2{\cdot}27$, $P = 0{\cdot}02$–$0{\cdot}05$, respectively), but the volumes of

these men's extracellular fluids were still slightly above normal. It has been suggested (*McCance*, p. 175) that the departures from the normal in the volume and composition of the urine of undernourished people who have been without fluids for 16 hours are the result of the abnormal composition of the body rather than any abnormality in the function of the kidney, so that this finding was perhaps only to be expected.

SUMMARY

1. Nineteen undernourished men whose ages ranged from 26 to 80 years were provided with unlimited amounts of food for eight weeks.

2. The kinds and quantities of food which they ate were recorded. Their average Calorie intake was 6,000 a day.

3. The average weight increased by 10 kg. during the eight weeks and the older men gained almost as much as the younger ones.

4. There was a significant rise in pulse rate, basal oxygen consumption, serum and blood volume, haemoglobin and haematocrit levels, serum protein concentration and cholinesterase activity as a result of the unrestricted diet. There was also an improvement in the concentration of the urine secreted after 16 hours without water.

5. There was little or no change in blood pressure and body temperature or in the incidence or degree of oedema.

6. The extracellular fluid volume was high at first, and there was a reduction in the absolute volume as well as in the volume expressed as a percentage of the body weight. There seemed to be little or no correlation between the volume of extracellular fluids and the amount of clinical oedema.

7. The men were examined periodically for two years after their return to the German rations. At the end of this time their weights were lower than they had been at the end of the experimental period, but their haemoglobin, haematocrit and serum protein levels were higher. Their oedema had almost disappeared.

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XXVIII. THE SIZE OF THE BABY AT BIRTH AND THE YIELD OF BREAST MILK

by R. F. A. Dean

INTRODUCTION

There is now good evidence that in some species the state of nutrition of the mother, particularly during the last part of the pregnancy when the foetus is growing very rapidly, has a definite effect on the size of the young at birth. This has been shown by experiment to be true for rats by King (1915) and for sheep by Wallace (1945). The only experimental work of the same kind which has been done on human mothers was undertaken in an effort to reduce the size of the foetus by restricting the diet during pregnancy. Kerr (1943) summarizes the work of five observers who dealt with a total of about 200 women, and there was general agreement that diet limited the size of the offspring. For information on a larger scale, the chief source must be the records of children born to mothers who for various reasons were ill-nourished in pregnancy. One of the earliest systematic attempts to determine the effect of nutrition on the size of the child was made by Smith (1916) who analysed data from London and Dublin hospitals. He recognized the difficulty of determining the state of nutrition of the mothers, and based his estimations on evidence obtained from three sources: the height/weight index, the impressions of the doctors who saw the women on their admission to the hospital for delivery, and the women's own accounts of their diets. The number of women thought to be badly nourished was small; he concluded, however, that a poor state of nutrition increased the percentage of dead babies and of babies born prematurely, and slightly decreased the average birth weight of full-term babies.

There were food shortages during and after the 1914–18 war and a great deal of evidence relating to the size of the babies born then was brought forward. Much of it was, however, inconclusive and even contradictory. Thus in the list given by Krogman (1941) there were 29 references to authors who reported that infants born during the war were smaller than normal and 26 to other authors who found no such alteration. In the period between the 1914–18 and the 1939–45 wars many surveys were undertaken to find out the effects of the consistently inadequate diets eaten by poor women in various parts of the world, and some of this work was summarized by Barcroft (1946) and by Garry and Wood (1946). The general conclusion was that the children born to mothers at the lower end of the socio-economic scale were usually a little below the average in size at birth, and that nutrition was probably one of the responsible factors.

As a result of the abnormal nutritional conditions created in many parts of the world by the 1939–45 war, opportunities again arose for observations on their effects on the size of the child at birth, and a few studies have been published. The observations can be grouped into two classes, according to whether the period of undernutrition was short and acute, or was prolonged and more chronic. Into the first class fall the studies made in Holland of the effect of the period of hunger lasting from September 1944 to May 1945, when the transport system was paralysed by a strike. Smith (1947a, b) found that there was a sharp decline in the weights of children born at the Zuidwal Hospital at The Hague and those attended by the nurses of the Midwifery School in Rotterdam, and that the reduction was closely related to the mothers' intake of Calories in the

last three or four months of pregnancy. The birth weights fell over the period from October 1944 to February 1945, but for no apparent reason the fall was then arrested although the food situation did not improve until May 1945. Large and small infants showed approximately the same percentage reduction, and the weights of infants of medium size were reduced by about 240 g. The lengths of the children were also reduced, but only by a small amount. Recovery was rapid, and by the beginning of July 1945 the pre-war level of weight had been regained. Confirmation of Smith's findings has recently been provided by Holmer (1949), who analysed data from the Gemeinteziekenhuis at The Hague, and reported that in the first half of 1945 the number of children under 3,000 g. at birth was 41·1 per cent of the whole; it had been only 24 per cent in 1942.

Antonov (1947) described the effects of the siege to which Leningrad was subjected from August 1941 until January 1943. This included a period of acute food shortage which lasted from September 1941 until February 1942, and 49 per cent of the 281 children born alive in the State Pediatric Institute in the first half of the year 1942 weighed less than 2,500 g. The average birth weight of the boys was 529 g. less than in the second half of the year 1941, and that of the girls was 542 g. less. Antonov said that similar reductions in average weight were found at clinics at Stalingrad at this time. He provided a summary of the findings of other Russian authors, who were concerned with famines such as those in Odessa in 1921 and 1922, and who observed similar reductions in birth weights.

The undernutrition experienced in Central Europe at the end of the 1939–45 war was mostly of the less acute type, but at the Italian Congress of Pediatricians held at Pisa in 1945, Frontali said that children born in Rome in 1944 were about 500 g. lighter than those born in 1936 and 1937. His figures have since been published (Scapaticci and Pappalardo, 1948). Husslein (1947) found that children born in Vienna in August 1945 weighed 600 g. less than those born in August, 1944. He did not find a similar reduction at Innsbruck, but he said that the food situation there was never so bad as it was in Vienna. Giese and Kayser (1947) reported that at the Landesfrauenklinik at Erfurt there was a more moderate reduction—about 230 g.—in the average weight of children born in 1946 as compared with those born in 1938. The year 1946 was worse than the year 1945, when the reduction was only 200 g.

The papers by Smith (1947a, b), to which reference has already been made, differ in several ways from other papers in which similar material is discussed. Smith did not, for instance, give average weights for all children together; instead he grouped the birth weights in ascending order of magnitude in successive periods and examined the different weights of the children occupying the middle positions and other positions in the arrays (see Table 3, p. 356). He says that "the entire phenomenon of birth weight decline, although of statistical significance, was apparent only when the data were analysed in this way". He had presumably found that crude average figures were misleading, and it is possible that the practice of relying on such figures may account for some of the discrepancies in the earlier reports. It is known that many factors have an important bearing on birth weight, and yet they have been disregarded by nearly all writers seeking to show differences caused by undernutrition. Smith realized, and in this he was almost alone, that great care should be taken to ensure that the various groups of mothers are strictly comparable.

It is universally accepted that boys are normally heavier than girls, and it is well known that first-born children are on average lighter in weight than those

born later (Vierordt, 1906; Harris, 1925; Stewart and Pratt, 1941). There has been some discussion as to whether weights of third and subsequent children exceed those of second children (Robertson, 1923; Harris, 1925; Martin, 1931), but this is unsettled. The effect of the age of the mother on birth weight is also uncertain, for although Murray (1924) and Martin (1931) were satisfied that their results showed no correlation, they cited a number of other writers who had been led to the opposite conclusion.

There is good evidence collected in different countries and over many years (Robertson, 1915; Martin, 1931; Karn, 1947) that the weight and length of the human child at birth are closely related to the time it has spent *in utero*. Growth is rapid in the last month of intra-uterine life, and according to Hamilton, Boyd and Mossman (1945), the foetus then gains about 45 mm. in length and 1,010 g. in weight; a small difference in gestation period will therefore have a comparatively large effect on the size at birth and particularly on weight. Prematurity is notoriously difficult to define exactly; the various so-called physical signs are not really conclusive and the League of Nations' standard is based on size. This may be satisfactory in normal circumstances, but it has obvious limitations if there is any interference with the development of the unborn child; abnormal circumstances might affect the weight of the child or the ability of the mother to retain the child *in utero* for the usual length of time.

There are some pathological conditions in pregnancy which tend to be associated with the birth of small children, chiefly because they are likely to shorten pregnancy. The most common of these conditions are pyelitis, hydramnios and the severer forms of pregnancy toxaemia. Difficulty in the actual delivery is often associated with the large size of the child, and alterations in the numbers of children delivered by caesarian section or by forceps would be consistent with alterations in the size of the children at birth.

There are many reports in the literature of the effect of undernutrition on lactation, and this is discussed by *Gunther and Stanier* (p. 379). None of these reports, however, has provided information about the actual amounts of milk given by a large number of women, and statistical treatment has not been attempted. Most authors have been content to express opinions, unsupported by figures. There is general agreement that ability to lactate is usually reduced, but that even in circumstances of exceptional hardship is not abolished altogether.

The birth weight has been shown to have a bearing on lactation, heavier children taking more milk than lighter ones on the fifth day (Stewart and Pratt, 1939). There is evidence that the age of the mother has an influence on her ability to lactate (König, 1939; Stewart and Pratt, 1939; Norval, 1947), younger mothers being usually more successful than the older. The advice given by Van Swieten in 1759 and quoted by Hamill (1903) to the effect that a good wet nurse should have borne several children suggests that multiparous women have for a long time been recognized as being able to provide more milk than women suckling their first children. Lactation may be established earlier in multiparae than in primiparae (Waller, 1947b), and at the end of the first nine to ten days the multiparae may already hold a slight but definite superiority (Wardlaw and Dart, 1932; Norval, 1947).

Anxiety certainly has a marked effect on lactation, and although the control of milk secretion is imperfectly understood, there is no doubt that the supply may fail under emotional strain. Similarly, suggestion is so powerful that it invariably complicates any attempt to assess the value of physical measures designed to improve the milk flow. In a severely undernourished

community, the women may have a strong desire to breast-feed their children because no other food is available and this may override the harmful effect of anxiety. It would explain why the number of Dutch women feeding their children was not reduced in 1944–5 (Smith, 1947b). In less exacting circumstances, unwillingness to breast-feed may be to blame for some lactation failures, and although Waller (1947a) was unconvinced by the evidence for this view, he pointed out that unwillingness must depend to some extent on the availability of adequate substitutes for breast milk.

"Much of the security of breast feeding depends on events during the earlier days of milk secretion" (Waller, 1943). Other writers (Norval, 1947; Robinson, 1943) agree with Waller, and it is common experience that any change in the circumstances of the mother is liable to disturb lactation. This is seen clearly in the comparatively large number of failures that coincide with the return of the mother to her own home after confinement. One of the reasons why a prolonged stay in hospital after delivery is advisable is that it allows a little extra time for the establishment of lactation. The value of good early lactation was put on a quantitative basis by Robinson (1947), who studied the milk output of 500 women who had given birth in St. Thomas's Hospital, London; she found that failure to lactate satisfactorily was rare if the child had been able to take more than 10 oz. of milk (about 280 g.) on the fifth day, and it is clear that this observation might be of considerable value as an index of probable success in breast feeding.

Freedom from disturbance is desirable for the mother, especially the mother of a first-born child, if she is to lactate well, and it is significant that the incidence of breast feeding has been found to be lower in women who have to share their houses with other families (Robinson, 1939; Mackintosh, 1944). Freedom from the necessity for too much physical exercise seems also to be advantageous because fatigue is believed to be unfavourable to milk secretion (Macy, Hunscher, Donelson and Nims, 1930; Robinson, 1943).

The influence of illness during pregnancy on lactation is variable, although it is generally agreed that the toxaemias, particularly eclampsia, are usually followed by poor lactation. The trauma inflicted during assisted delivery may also hinder lactation because of its effect on both mother and child.

The weight gains in early life depend upon the weight at birth, the physiological loss of weight in the first few days and the amount of milk which the child takes. If any of these is influenced by undernutrition, the speed at which the birth weight is recovered would probably also be affected. The weight at the end of the first week is largely independent of any treatment intended to counteract the physiological loss (Roscoe, 1949).

The present investigation consists of an analysis of the records of the Landesfrauenklinik der Rheinprovinz in Wuppertal for the period 1937 to 1948. The first section gives an account of the way the information was collected. The results of various comparisons, such as the lengths and weights of the babies, and the amounts of breast milk taken, are given in the second section, with a consideration of various factors which may have had some bearing on the results.

THE COLLECTION OF THE EVIDENCE

In June 1946, through the courtesy of Professor Anselmino, the Unit was given access to the Obstetrical Departments of the Landesfrauenklinik, Wuppertal and to their records. The Klinik was a teaching centre for midwives,

the nursing and obstetric care was good, and the general impression was one of order and efficiency. The work of rebuilding, extension and reorganization, which had been undertaken by Professor Anselmino when he was first appointed Director, was completed in 1937. That year was taken as the starting point of the present investigation partly for this reason, and also because it was the last year of normal peacetime conditions. By 1937 the Klinik had established itself so favourably in the life of the community that all classes were seeking admission. The reputation gained then was maintained, and in 1946 it seemed to be generally agreed that if any change had occurred since 1937 in the social status of the women, it was in the direction of improvement. This was confirmed by the alterations in the proportion of private patients, which rose from 5 per cent in 1937–8 to 22 per cent in 1945–6, and in the proportion of women given free board and medical care in return for domestic work in the Klinik, which fell from 22 per cent in 1937–8 to 5 per cent in 1945–6. But by 1946 a much greater proportion of the Wuppertal women were asking for hospital delivery. This was not entirely due to the raising of the esteem in which the Klinik was held; it was certainly also a result of the deterioration of home conditions, and the overcrowding which had become so common. The total number of births in the town of Wuppertal for some of the years under review, and the percentage of the births that took place in the Landesfrauenklinik are given in Table 1.

TABLE 1

Total number of children born in Wuppertal and percentage born in the Landesfrauenklinik

	1937	1938	1946	1947	1948
Total number of children born in Wuppertal ..	5,824	6,380	3,458	3,624	3,667
Percentage of total born in the Landesfrauenklinik ..	20	20	70	51	51

The figures are not exactly correct because a small number of women who lived outside the town but were delivered in the Klinik are included. There was, however, an enormous difference between the early and late years, and it is interesting that a similar, but much smaller, rise in the number of women seeking hospital confinement occurred in England during the 1939–45 war (Waller, 1947a).

It is curious that, although there was undoubtedly a desire for hospital confinement amongst the Wuppertal women in 1945–6, there was no corresponding attempt on the part of the mothers to prolong their stay after their children were born. According to the Klinik authorities, the mothers were urged to stay the usual ten to eleven days, but most of them refused. The last statement is undoubtedly true. In 1937, 91 per cent of the women were still in the Klinik on the ninth day after the delivery of their children, but in 1946 the percentage had fallen to 81. There can be little doubt that for many of the women the conditions at the Klinik were more favourable for both themselves and their children than at home, and it can only be concluded that the women were convinced of the necessity for returning home at the earliest opportunity because they felt they were badly needed there.

It was the practice of the Klinik to weigh and measure the children in the labour ward within a few minutes of birth. Subsequently the children were weighed in their nurseries before and after every feed. The milk record was carefully kept, and included details of the amounts and nature of all supplementary feeds. The ordinary records of the Klinik were remarkably complete. The form filled in for each mother included details of the past medical and obstetric history, as well as those of the examination on admission and the progress during labour, delivery and the puerperium. This form was the chief source from which the statistical data were compiled. For the 1946 births, it was supplemented by a card which was filled in by one of the women doctors of the Klinik whose services were placed at the disposal of the Unit. The card was designed so that all the information in the Klinik's records about the mother and her child could be collected together, and some additional information might be included, such as the adequacy of her diet during pregnancy and her weight at various times. When she left the Klinik, another card was written and was sent through the town child welfare organization to the local office where she would be expected to attend each month for the weighing of her child and for the issue of the coupons for the supplementary rations granted during lactation (*Gunther and Stanier*, p. 379). The card was intended to provide a record of the weight of the child and the manner in which it was fed. For various reasons, only about one-third of these cards was completed and returned to the Unit.

As shown in Table 2, the total number of births in the Landesfrauenklinik in each of the years 1937 and 1938 was about half the number in 1945 and 1946. Living conditions in 1937 must have been very similar to those in 1938, and for most purposes the data for these years have been amalgamated. The years 1945 and 1946 have usually been dealt with separately, because they were in some ways different. All births, whether live or dead, of single or twin infants, with or without operative interference, have been included in the general figures, except where some statement to the contrary is made. Similarly the lactation records relate to all mothers whose children remained alive whilst they were in the Klinik. The abnormal deliveries and the unusual lactations have received some special analysis, but since it was desirable to present an overall picture, they could not be excluded. Various systems of selection were tried, but they all involved definitions of what was to be regarded as the normal or the abnormal and were therefore unsatisfactory.

Data for boys and girls, and for first-born and other children, have always been analysed separately, and have only been amalgamated where it seemed justifiable to do so. For the purposes of the present investigation, a primiparous woman has been defined as one who according to the records of the Klinik, had not had any previous pregnancy. If there was a record of abortion or miscarriage the mother was placed in the category of multiparae.

The length of the period of gestation was found by calculating the number of days that elapsed between the beginning of the last menstrual period and the birth of the child.

THE STATE OF NUTRITION OF WOMEN IN WUPPERTAL AFTER THE WAR

The Diets

The observations of the Unit began in June 1946 and at that time food was difficult for the normal consumer to obtain in adequate quantities. Some

TABLE 2

An analysis of births at the Landesfrauenklinik between 1937 and 1948

Year	Total number of children	Percentage of boys	Percentage of girls	Average weight boys *less* average weight of girls (g.)	Percentage of first births	Percentage of later births	Average weight of later-born *less* average weight of first-born children (g.)
1937	1,144	52·7	47·3	115	52·1	47·9	125
1938	1,290	51·8	48·2	115	48·9	51·1	125
1939	1,715	53·0	47·0	145	48·3	51·7	195
1940	2,114	51·4	48·6	115	47·8	52·2	175
1941	1,985	53·5	46·5	145	52·4	47·6	140
1942	1,759	51·7	48·3	130	48·1	51·9	180
1943	1,809	53·6	46·4	160	49·6	50·4	215
1944	2,602	51·6	48·4	155	57·6	42·4	160
1945	1,906	53·3	46·7	120	58·3	41·7	105
1946	2,438	50·4	49·6	95	53·2	46·8	145
1947	1,862	50·9	49·1	125	48·8	51·2	180
1948	1,821	52·1	47·9	110	50·0	50·0	215
1937–8 (together)	2,434	52·2	47·8	115	50·4	49·6	125
1945–6 (together)	4,344	51·8	48·2	105	55·5	44·5	130

effects of the shortages must have reached the mothers, although sentiment and the extra rations they were allowed may have afforded a certain amount of protection. The time of the most acute food shortage was, however, said to have been in 1945. If this was true and if undernutrition had any effect on the mothers and their children, the effect should have been at its maximum in that year.

It was impossible to find out the actual amounts of food eaten by the Wuppertal men and women living at home. Accounts of the official rations and of the supplements granted to pregnant and lactating mothers are given by *Gunther and Stanier* (p. 379). In the latter half of 1946, women were in theory entitled to about 2,400 and 3,500 Calories a day during pregnancy and lactation respectively. The amount of food they actually received depended upon many things, such as the availability of the rations in the shops, and the demands of the other members of the family, particularly of the children. It depended also upon their ability as foragers, their energy, their connexions with people in districts with surplus food and the skill of their husbands as gardeners (*McCance and Widdowson*, p. 1). Some idea of the situation can be obtained by an analysis of the replies given by the women delivered during the second half of 1946 when they were questioned at the Landesfrauenklinik. Thirty-one per cent said that they were able to get the whole of their rations, but nothing more. Twenty-three per cent admitted to obtaining more than the ration, and 46 per cent complained of receiving less. They were asked which articles of food they had failed to obtain, and which they had been able to procure in excess of the ration. Foods included in this inquiry were potatoes, vegetables, fruit, milk, cheese, fat, meat and bread. It was found that the extras the women had most usually been able to get were fat, potatoes and vegetables. One out of every three of the extras was fat, and one of every six, potatoes or vegetables. Extra amounts of other foods were obtained in the following order of frequency: fruit, meat, milk, bread and cheese.

Complaints about the rations not being honoured chiefly related to fat, milk and potatoes. Of the other foods, cheese, meat and bread gave the least difficulty, but the rations of the first two were very small.

Body Weights

When the women delivered in 1946 were questioned about their weights, most of them knew their normal weights before there were any food restrictions, but very few could say what they had weighed at the beginning of pregnancy. About 150 had been weighed at the beginning of the 8th and 9th months, and they were all weighed at the Klinik at the beginning of labour, and again 8–9 days after delivery.

The data obtained from the 150 women have been compared with those given by Stander and Pastore (1940). These authors estimated the weight increases during pregnancy of nearly 3,000 women who were delivered in a New York hospital, and found that by the end of the 40th week the average increase was 24·1 per cent of the weight before the pregnancy began. They were able to calculate the percentage increment for each week from the 6th to the 40th, and also the amount of the losses that occurred in the week before labour, during delivery and by the end of the first 10 days of the puerperium. They found that primiparae and multiparae had the same weight changes, and that in severe toxaemia the gains before delivery, and the losses after, were excessively high.

The Wuppertal figures were tested to see if they corresponded with the American, in the hope that it might be possible to calculate the probable

weights of the women at the start of the pregnancy; comparison with the weights which the women had given would then provide some indication of the amount of weight that had been lost. The attempt was made because there was no other way of finding out the extent of the loss, and although it was realized that the answer would at best be approximate.

The data were plotted in scatter diagrams showing the relationship of the weights at the beginning of the 8th month to the weights at the beginning of the 9th month, at the onset of labour, and at the end of the stay in hospital on the 8–9th day of the puerperium. The scatter was very evenly distributed on either side of the averages given by Stander and Pastore, and it was therefore assumed that the gains between the 8th month and the time of the birth were normal in amount. It seemed reasonable in the circumstances to suppose that the gains from the time of conception had not been grossly abnormal. The non-pregnant weights of the 105 women who had given their previous normal weights were calculated from the records of their weighings, using the constants provided by Stander and Pastore, and it was found that they had apparently started their pregnancy when about 9 per cent under their normal weights. This was a reasonable figure, which agreed with other findings of the Unit.

RESULTS

Weights and Lengths at Birth

The average birth weights of all the children born in the Landesfrauenklinik during the years 1937–48 are shown in Fig. 1. The ratio of boys to girls remained fairly constant throughout the 12-year period (Table 2), but there were fluctuations in the proportion of first-born and later-born children. The figure also gives the average weights of boys and girls and of first- and later-born children. All the curves show the same tendency. The first sign of a definite fall was in 1940. The birth weights then remained steady until 1944, but in 1945 there was a further and much greater fall. Afterwards there was a steady rise until 1948 when the 1940–44 weight was regained. The average birth weight for all children between 1937 and 1939 was about 3,340 g. In 1940 it fell to 3,290 g., and in 1945 to 3,155 g. The total fall was therefore 185 g. The drop at the end of 1939 coincided with the outbreak of war, and that in 1945 with the period of most acute food shortage at and following the end of the war.

Fig. 1 clearly shows that boys were always heavier than girls, and later-born children heavier than first-born. The actual differences between the weights are given in Table 2. These differences fluctuated, but not in a consistent manner; on the whole, rank of birth made more difference to birth weight than sex did, but the fall of 185 g. in the average birth weight of all children between 1939 and 1945 is greater than could possibly be accounted for by any of these fluctuations.

In Fig. 1 the average weights for the whole years are shown. The averages for each quarter-year have also been calculated, but do not provide evidence of any cyclic variation in birth weight. The lowest average weight (3,190 g.) was reached during the second quarter of 1945. The third and fourth quarters of that year showed rapid recovery.

Because of the possibility that the averages might be misleading, the data for the two-year periods 1937–8 and 1945–6 have been examined by the method of grouped frequency distribution, and in Fig. 2 the percentages of children falling into seven categories of birth weight are shown. These pairs of curves have a similar trend, which is the same for the children of each sex and for those of

primiparous and multiparous mothers, and it is clear that more small babies were born in the later years. This is shown by the tendency for the 1945–6 curve

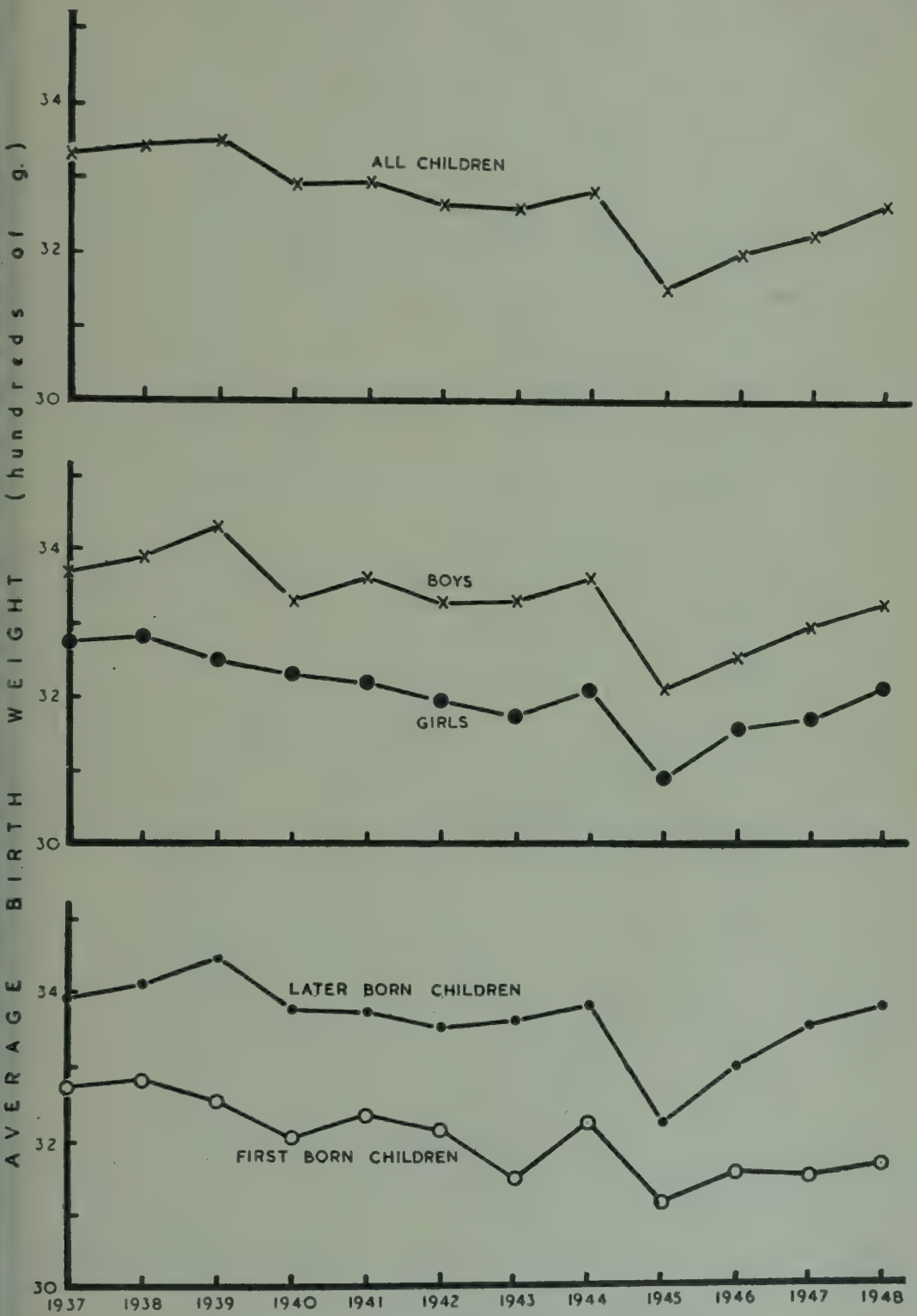

FIG. 1. Average birth weights: 1937 to 1948.

to remain on the left-hand side of the other. The differences between the figures for the two two-year periods are in each case statistically significant.

TABLE 3

*Weights of children born in Wuppertal and The Hague analysed by the method of percentiles**

	Wuppertal					The Hague		
Percentile	1937–8 weight (g.)	1945 weight (g.)	Fall from 1937–8 to 1945 (g).	1946 weight (g.)	Fall from 1937–8 to 1946 (g.)	1938–9 weight (g.)	4.1.45 to 15.4.45 weight (g.)	Fall from 1938–9 to 1945 (g.)
10	2,800	2,630	170	2,730	70	2,920	2,680	240
25	3,100	2,950	150	3,000	100	3,130	2,910	220
50	3,400	3,250	150	3,300	100	3,440	3,200	240
75	3,710	3,550	160	3,600	110	3,760	3,440	320
90	4,000	3,850	150	3,900	100	4,000	3,640	360

*For this analysis, the weights of the children born in each of the years were placed in lists in ascending order. The lists were then divided into a hundred parts and the weight of the child who occupied the 10th, 25th, 50th, 75th, and 90th position (or "percentile") was ascertained for each year.

In Table 3 are shown the results of arranging the children born in 1937–8 and in 1945 and 1946 in order of birth weight, and finding the weight of children

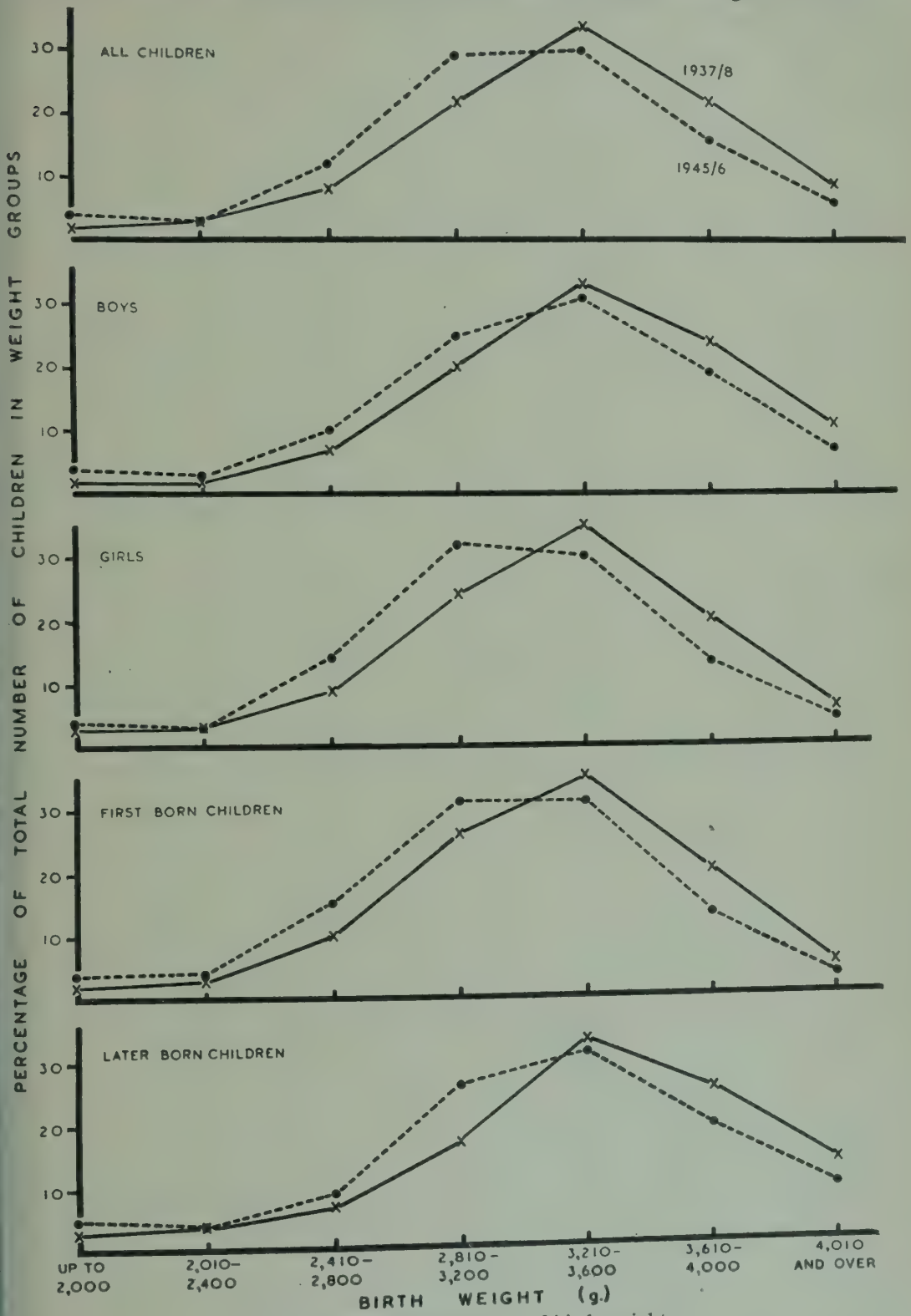

FIG. 2. Frequency distribution of birth weights.

at selected points in the order (the method of "percentiles"). In Wuppertal the reduction in weight was greater at each percentile in 1945 than in 1946, which is

TABLE 4

Analysis of births of children weighing less than 2,400 g.

Period covered	Weight (g.)	Number of children	Percentage of total number of children	Twin children		Non-twin children	
				Number born	Percentage who died in first 8 days	Number born	Percentage who died in first 8 days
1937–8	Up to 1,600	29	1·2	2	50	27	86
	1,610–2,000	23	1·0	8	50	15	40
	2,010–2,400	51	2·1	10	30	41	12
1945–6	Up to 1,600	131	3·1	35	60	96	80
	1,610–2,000	62	1·4	11	45	51	41
	2,010–2,400	120	2·7	9	22	111	11

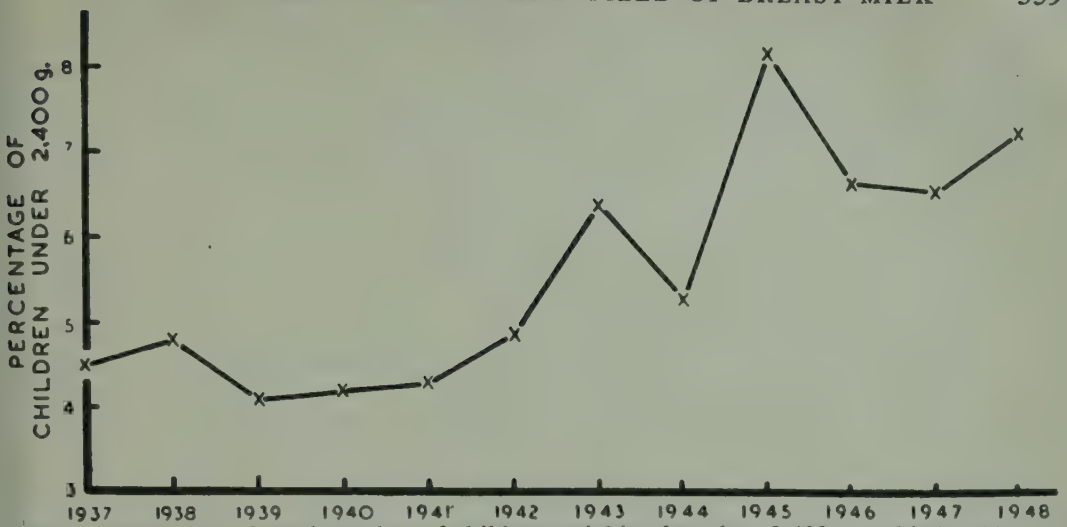

FIG. 3. Percentage of total number of children weighing less than 2,400 g. at birth, 1937 to 1948.

in agreement with the average birth weights. The light and the heavy children all showed approximately the same reduction. The pre-war figures from The Hague (Smith, 1947a) are higher than the 1937–8 Wuppertal figures, and the reductions in 1945 were much greater at The Hague.

In Fig. 3 the percentage of children under 2,400 g. at birth in each of the years from 1937 to 1948 is given. The number was approximately constant until 1941, but then rose until it reached its maximum in 1945. The birth weights under 2,400 g. have been analysed further (Table 4). There was no increase in the percentage of deaths up to eight days after birth, and if we assume that the care of the premature infant was not greatly improved in 1945–6, we must conclude that the smallest babies born in these years were as well fitted to survive as those born in 1937–8. The incidence of stillbirths and malformations was the same in 1937–8 as in 1945–6 (Table 5).

TABLE 5

Abnormalities of pregnancy, delivery and puerperium 1937 *and* 1938: 1945 *and* 1946

(Percentage of total number of births)

Abnormality	1937	1938	1945	1946
Pyelitis	4·7	3·3	5·1	7·5
Eclampsia ..	0·4	0·4	0·2	0·5
Other toxaemias of pregnancy ..	1·1	1·8	2·3	1·7
Hydramnios ..	0·5	0·6	0·6	0·5
Stillbirths	1·8	2·2	1·8	1·8
Malformations ..	1·7	1·4	1·8	1·7
Forceps delivery ..	8·1	7·8	2·7	3·0
Caesarian section	3·7	5·3	1·9	1·2
Severe post-partum haemorrhage ..	1·8	1·9	2·1	4·4
Mastitis (needing incision)	1·4	1·9	1·0	1·1
Endometritis ..	3·6	4·7	3·7	4·3

Fig. 4 shows the percentage of first-born, second-born and later-born children falling into the seven categories of birth weight in 1937–8 and in 1945–6. In 1937–8 the second-born children were significantly lighter than those born subsequently, but this was not so in 1945–6. It seems that one of the effects of

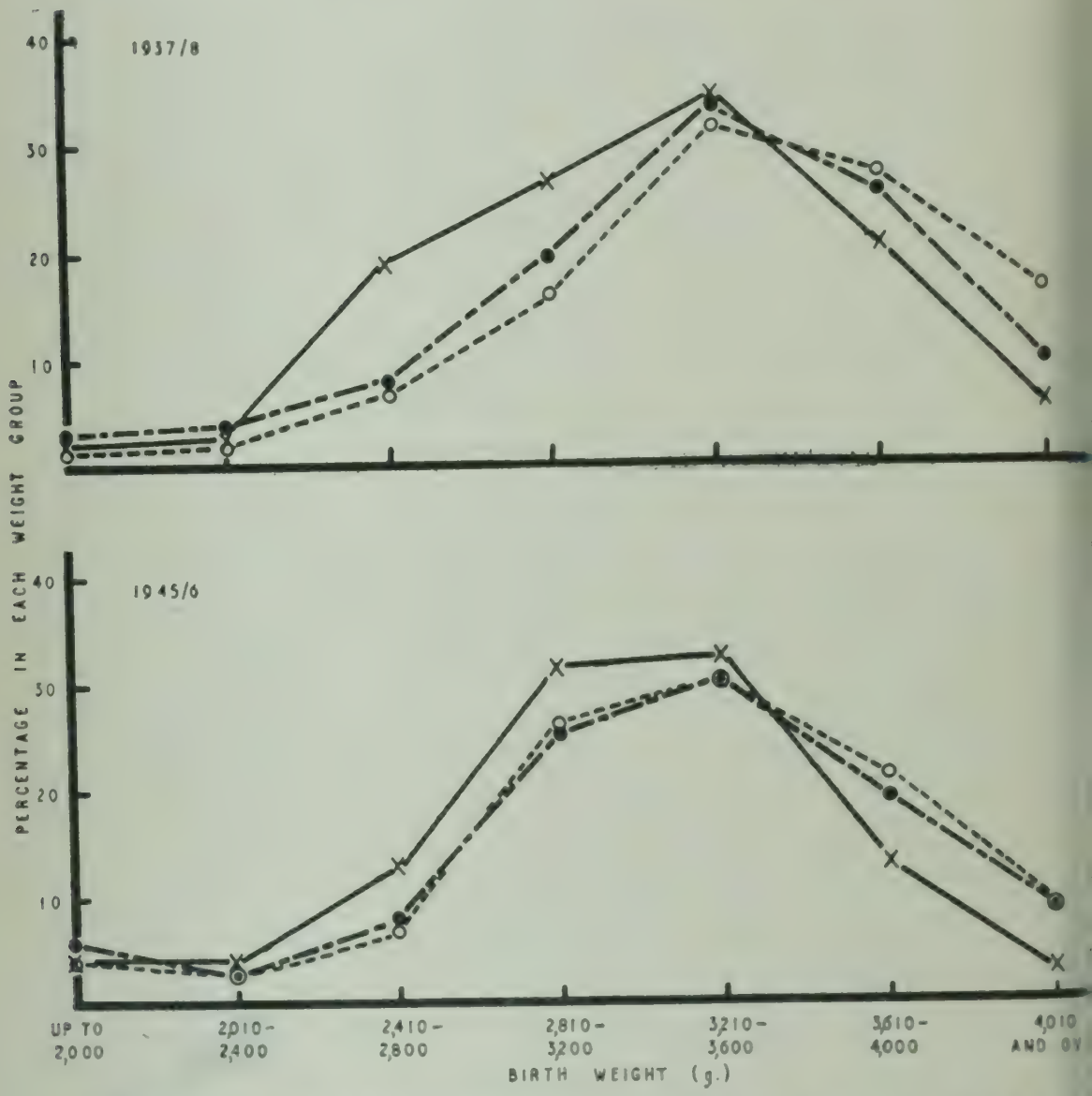

FIG. 4. Effect of rank in the family on birth-weight, 1937/8 and 1945/6. ·——· first-born children; ●– – –● second-born children; O- - -O later-born children. Difference between means/S.E. of difference: for (*a*) first-born/second-born = 8·89 for 1937/8, 5·96 for 1945/6; (*b*) second-born/later-born = 3·55 for 1937/8, 0·99 for 1945/6. The differences are significant in all except the last instance.

the conditions in 1945–6 was the removal of this difference, but as the cause of the difference is unknown, no explanation can be offered. It was not due to changes in the proportion of boys and girls, which was the same for first-born and later-born children in 1937–8 as it was in 1945–6.

The average birth weight of the children of private patients was somewhat greater than that of the other children born in the Klinik (Table 6). The increase

therefore, in the proportion of private patients in 1945-6 (see p. 350) must have tended to raise the average birth weight of the children born in the Klinik in those years and so to mask somewhat the magnitude of the fall attributable to undernutrition.

TABLE 6

Comparison of average birth weights of children of private and other patients

Year	Weight of children of private patients (g.)	Weight of other children (g.)
1937/8	3,495	3,330
1945	3,325	3,103
1946	3,414	3,213

The percentages of children falling into different categories of length at birth are shown in Fig. 5 (p. 362). In each subject there was a slight tendency towards shorter children in 1945–6 and the figures from which the curves are drawn are significantly different when analysed statistically. The average length of all the children in 1937–8 was 50·17, and in 1945–6, 49·99 cm. The difference was therefore 1·8 mm.

Smith (1947a) analysed his data for length at birth in a different way, and found that the number of children under 50 cm. long in the pre-war period was 10 per cent of the whole. In the period of hunger, the percentage increased steadily for six months and in the first quarter of 1945 was about 42. The highest percentage reached in Wuppertal was 32 in the second quarter of 1945, as compared with 18 per cent before the war. The lengths of the babies were therefore most affected at the time when the birth weights were at their lowest.

There was no increase in the incidence of diseases which tend to shorten pregnancy and therefore to lead to the birth of small children (see Table 5). The average period of gestation was slightly shorter in 1945–6 than in 1937–8. The reduction amounted to 1·25 days and this according to Hamilton *et al.* (1945) would account for about 45 g. in weight and 2 mm. in length, which is a little more than one-fourth of the actual reduction in weight and almost exactly the reduction in length. In Fig. 6 (p. 363) the frequency distribution of different gestation periods shows a small but consistent tendency to a shorter gestation period in 1945–6. The differences between the means of the figures for each pair of curves are statistically significant.

The percentages of the total number of mothers falling into different age groups in 1937–8 and 1945–6 are shown in Fig. 7 (p. 364). In 1945–6 a larger proportion of women aged under 26 and over 31, gave birth in the Klinik. The differences are highly significant according to statistical definition, and it has therefore been necessary to consider the relationship between the age of the mother and the size of the child. The consideration has been limited to

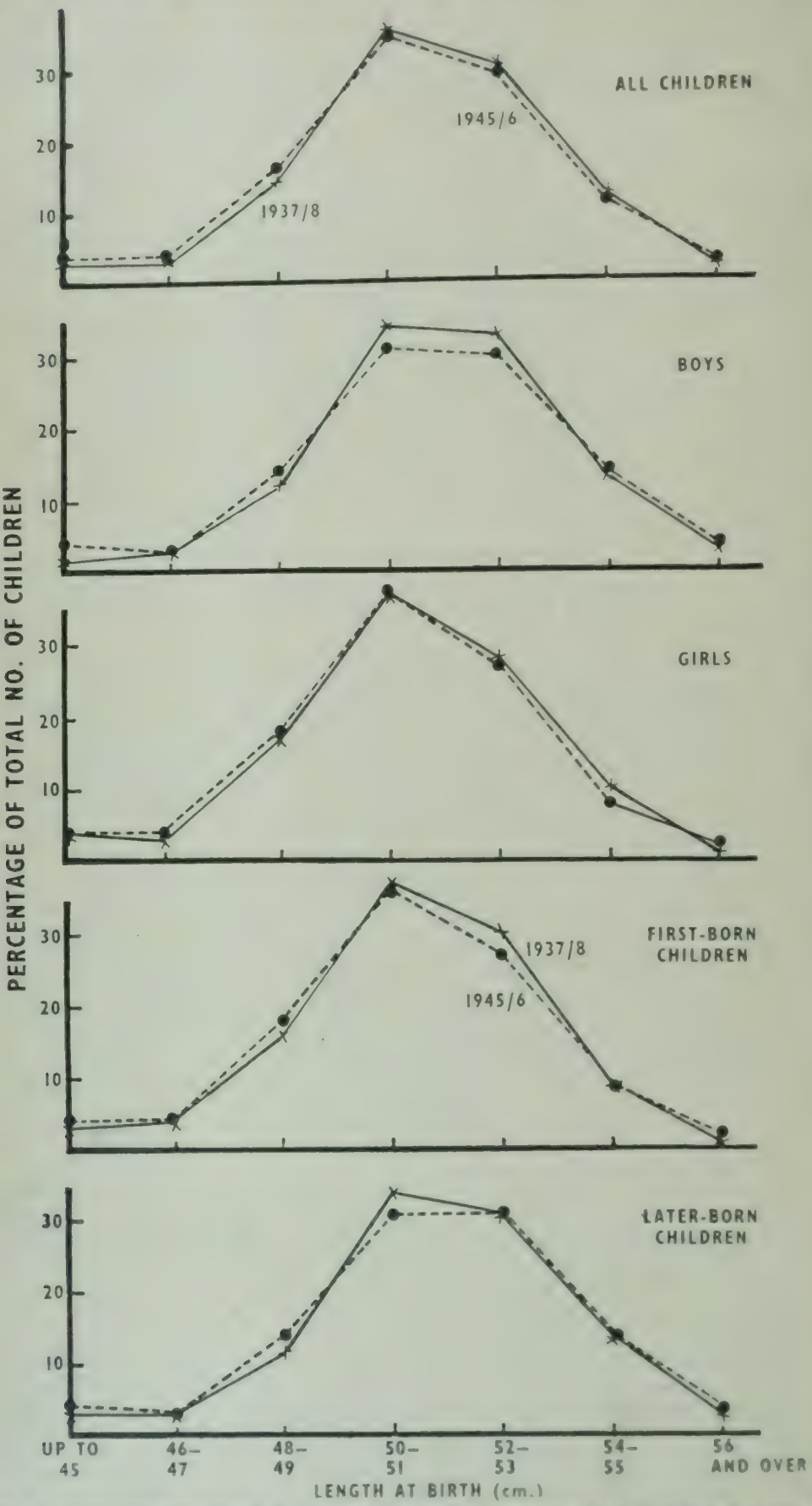

FIG. 5. Frequency distribution of lengths at birth, 1937/8 and 1945/6. For 'all children' the difference between the means/S.E. of difference is greater than 2.

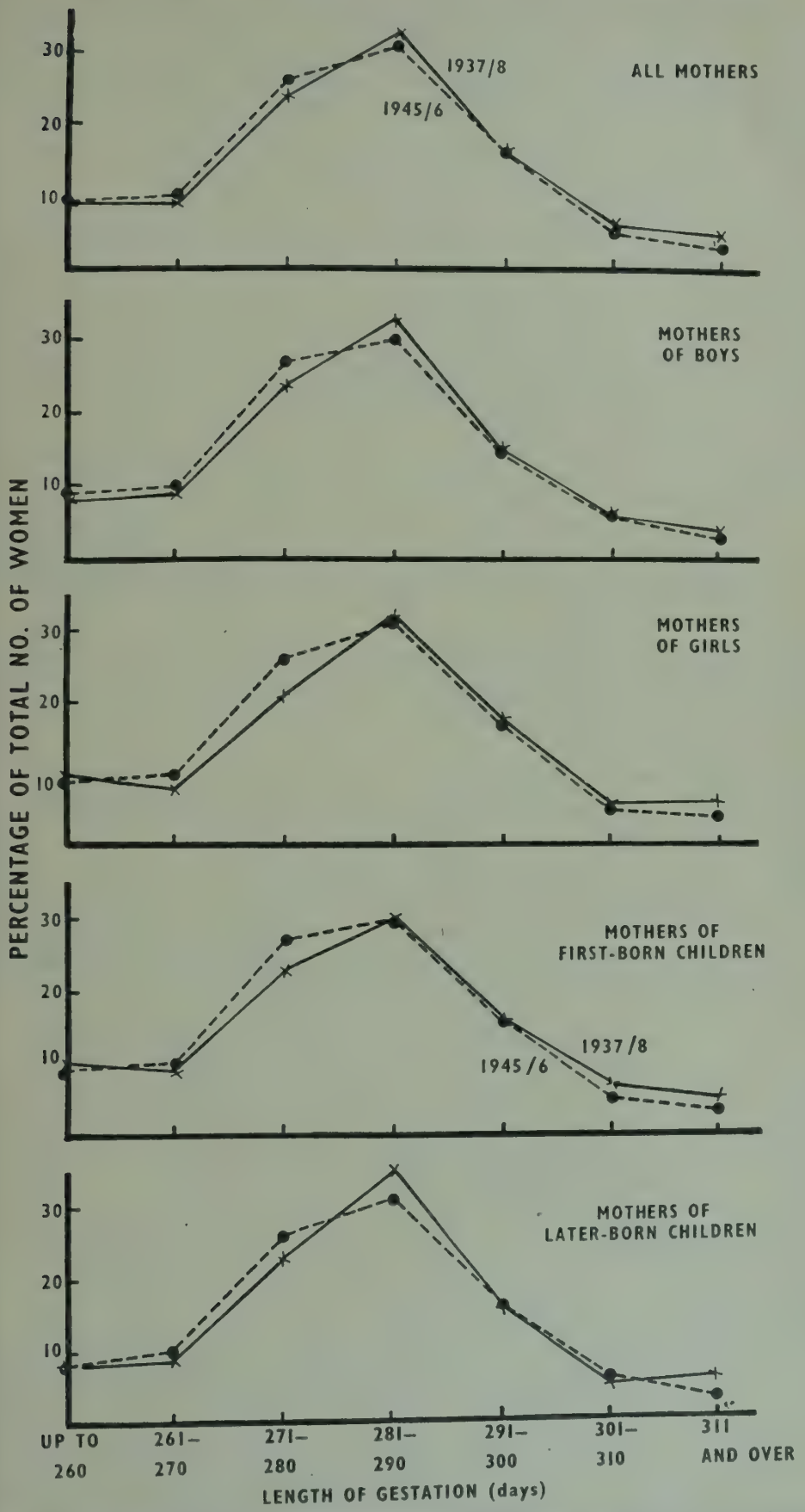

FIG. 6. Frequency distribution of gestation periods, 1937/8 and 1945/6. For 'all mothers' the difference between the means/S.E. of difference is greater than 2.

primiparae because of the complications introduced by multiparity. The effect of the age of the mother on the birth weight of her first baby is shown graphically in Fig. 8. The curves do not suggest that there was any correlation in any of the four years, 1937 and 1938, 1945 and 1946, and this is borne out by statistical analysis as shown below the Figure.

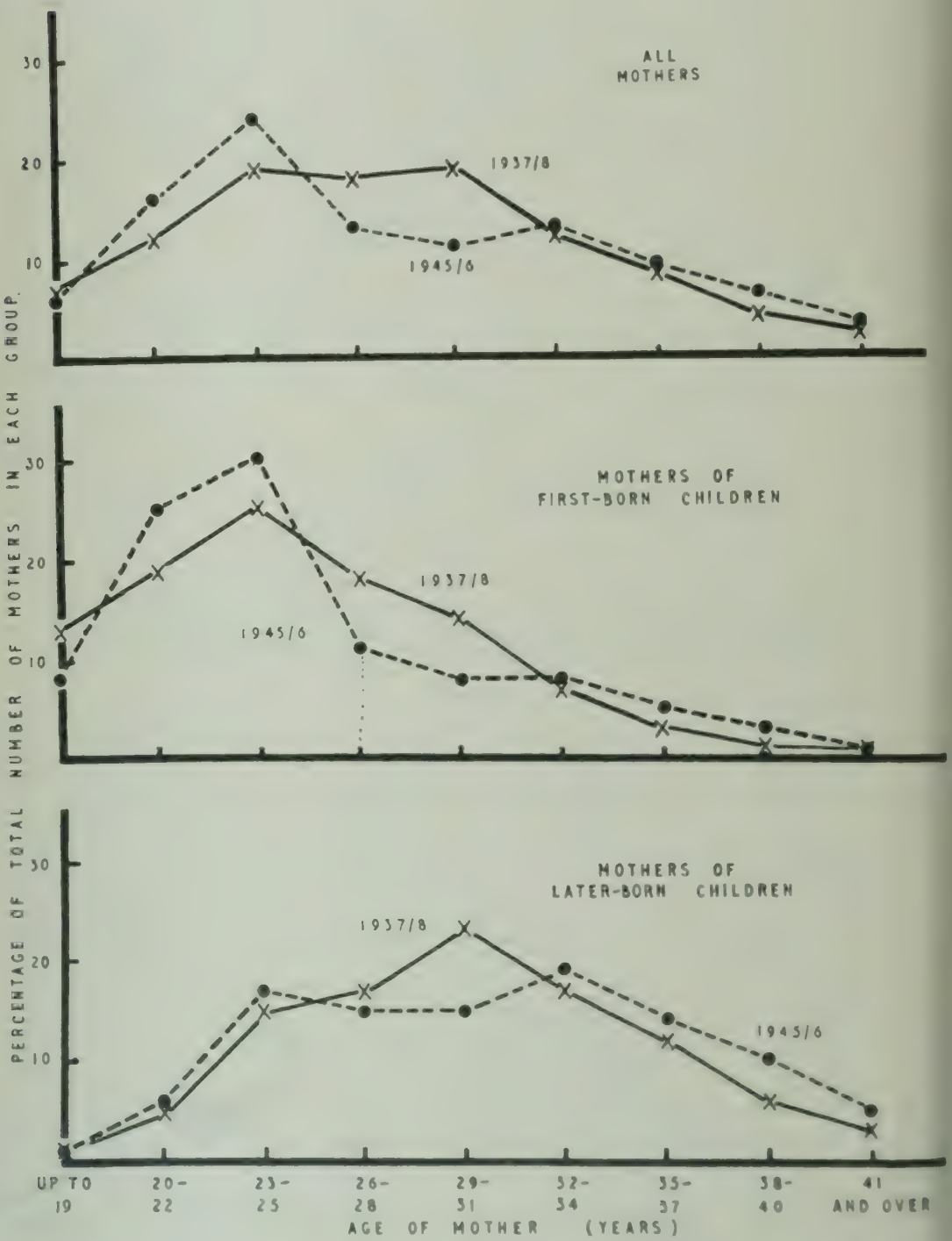

FIG. 7. Frequency distribution of ages of mothers, 1937/8 and 1945/6. For all mothers $\chi^2 = 94{\cdot}0$, $P = <0{\cdot}001$.

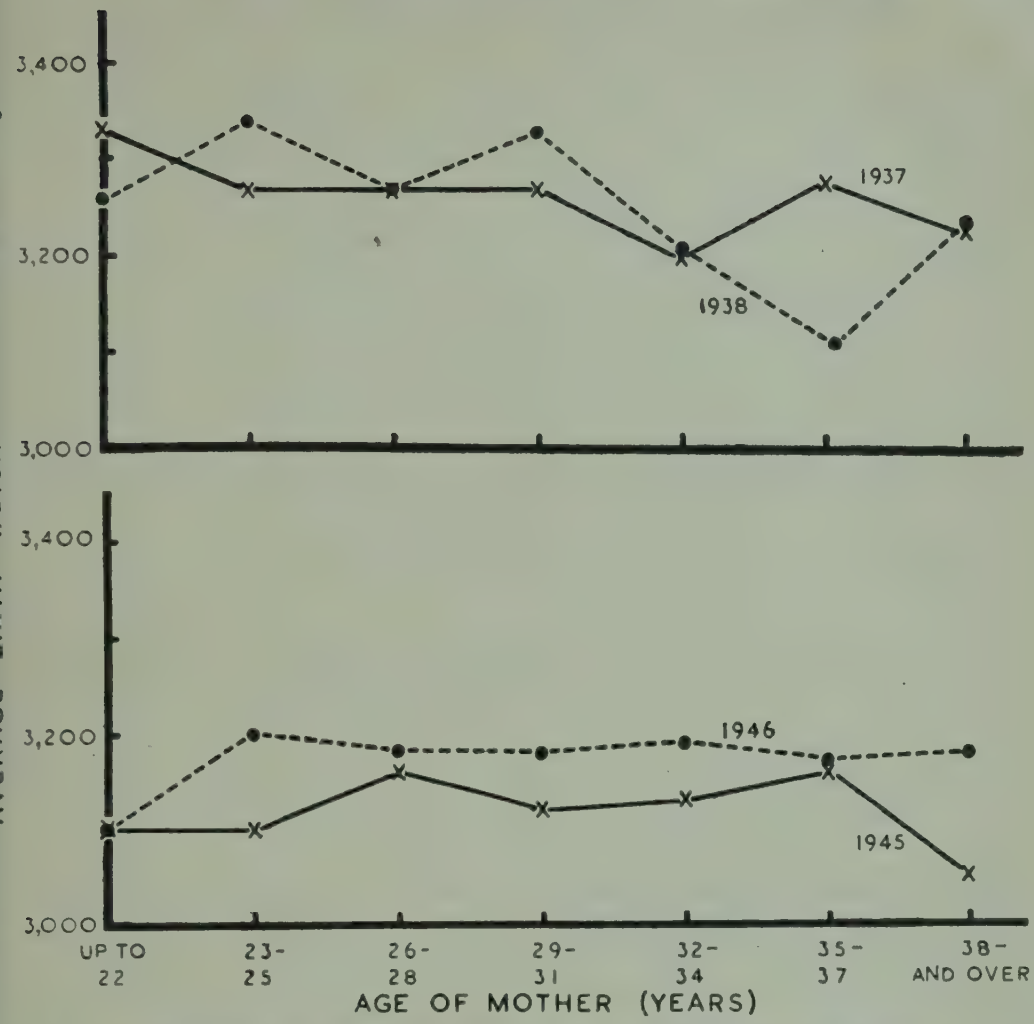

FIG. 8. Relation between the age of the mother and the birth weight of her first child: 1937 and 1938, 1945 and 1946.
The coefficient of rank correlation (Kendall's τ) has been calculated for the four years. τ was +0·14 and +0·43 for 1937 and 1938, and −0·19 and −0·50 for 1945 and 1946. None of these values are significant at the 5 per cent level.

Early Lactation

In Table 7 is shown the average amount of milk taken by the children on the fifth to ninth days of life in 1937 and 1938, 1945 and 1946. It is remarkable that the figures for 1938 are consistently about 25 g. lower than those for 1937. In 1938 the rationing system was introduced for the first time, but it applied only to butter and the ration was large. There would seem to be no nutritional reason for the reduction in the amount of milk in 1938, and no adequate explanation can be offered.

The figures for 1945 show that in this year the milk taken was on average about 80–90 g. less on each day than in 1937. There was a very slight improvement in 1946 which was proportionally smaller than the recovery in birth weight.

Table 7 also indicates that:

(*a*) The average amount of milk taken by first-born children was a little less (about 20 g.) than that taken by children born later.

(*b*) The amount of milk taken increased from the fifth to the eighth day, but did not usually increase again on the ninth day.

TABLE 7

Average milk yield

(g./day)

Year	Sex of child	5th day		6th day		7th day		8th day		9th day	
		Primi-parous mothers	Multi-parous mothers	Multi-parous mothers	Primi-parous mothers	Primi-parous mothers	Multi-parous mothers	Primi-parous mothers	Multi-parous mothers	Primi-parous mothers	Multi-parous mothers
1937	M.	312	326	353	358	390	390	398	405	403	399
	F.	306	349	346	392	371	422	382	440	382	418
	M. and F.	309	337	350	374	381	406	390	422	394	408
	All children	322		361		393		405		400	
1938	M.	291	311	332	353	355	375	377	399	369	368
	F.	276	307	326	340	354	372	361	388	358	378
	M. and F.	284	309	330	347	355	373	370	394	364	373
	All children	297		338		363		382		368	
1945	M.	226	258	263	290	278	314	306	322	302	326
	F.	223	260	259	283	276	300	288	322	294	311
	M. and F.	225	259	261	287	277	308	298	322	298	319
	All children	238		267		289		308		307	
1946	M.	234	252	277	287	297	304	313	323	322	347
	F.	240	255	271	291	293	315	311	327	326	339
	M. and F.	237	253	274	289	295	310	312	325	324	343
	All children	245		281		297		320		332	

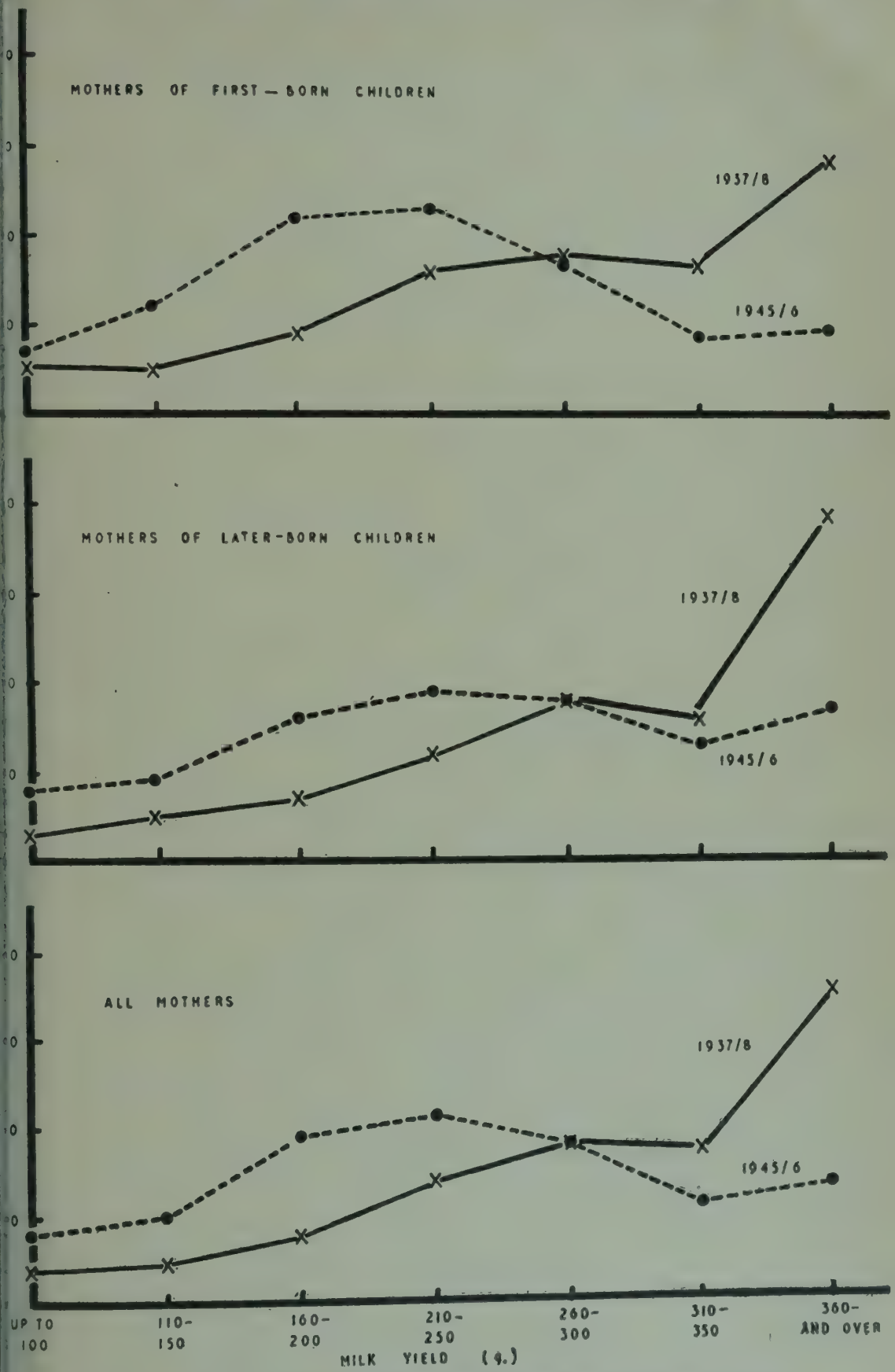

FIG. 9. Frequency distribution of milk yields on 5th day, 1937/8 and 1945/6.

(*c*) The daily increases were at their largest between the fifth and sixth days and diminished later.

In Fig. 9 the distribution of the percentage of mothers giving small and large amounts of milk on the fifth day is shown to be greatly different in the two biennial periods. In 1937–8 a much larger proportion of women were in the groups giving more milk.

The percentages of the total number of mothers who in the years 1937 to 1948 satisfied the criterion advanced by Robinson (1947) for successful early lactation i.e. 280 g. or more per day are shown in Fig. 10. The percentage fell steadily from 67 in 1937 to 31 in 1945. It then rose, and reached 43 in 1948. The results shown in Figs. 9 and 10 confirm the conclusions drawn from the averages already given for milk yield in 1937–8 and 1945–6 (Table 7).

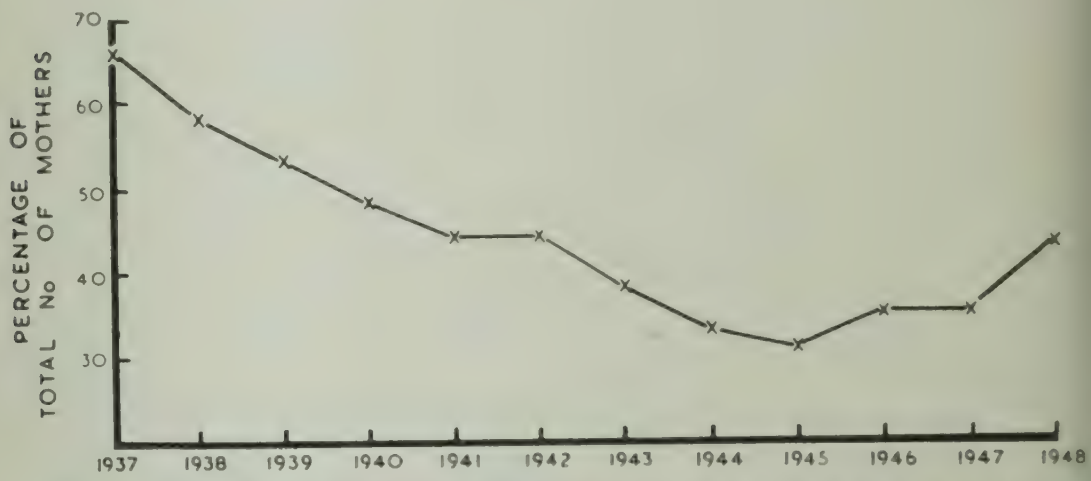

FIG. 10. Percentage of total number of mothers giving 280 g. milk or more on 5th day.

The relation between birth weight and milk yield on the fifth day is seen in Fig. 11. In both two-year periods the larger children took the most milk, but children born in 1937–8 always took more milk than children of the same birth weight born in 1945–6.

Fig. 12 shows that there was a clear relationship between the age of the primiparous mothers and the amount of milk they were able to provide on the fifth day; the young mothers were much more successful than the old. The effect was apparent in both 1937–8 and in 1945–6, but it was more marked in the earlier years. The Figure also provides further confirmation of the fact that mothers having their first babies in 1937–8 were able to feed them more successfully than those whose first babies were born in 1945–6. This was true whatever the age of the mother.

Abnormalities of the puerperium which might have affected lactation did not increase in the later years (Table 5, p. 359), but the treatment of infective conditions such as mastitis and endometritis was certainly better in 1945–6 because of the introduction of the sulphonamide drugs; penicillin was not available until later. There was a decline in the percentage of abnormal deliveries for which there may have been several reasons. In 1937–8 the potentially abnormal cases formed a larger proportion of the total admissions to the Klinik than in 1945–6, because in the later years so many women sought to be delivered there instead of at home for reasons which were not primarily medical. The

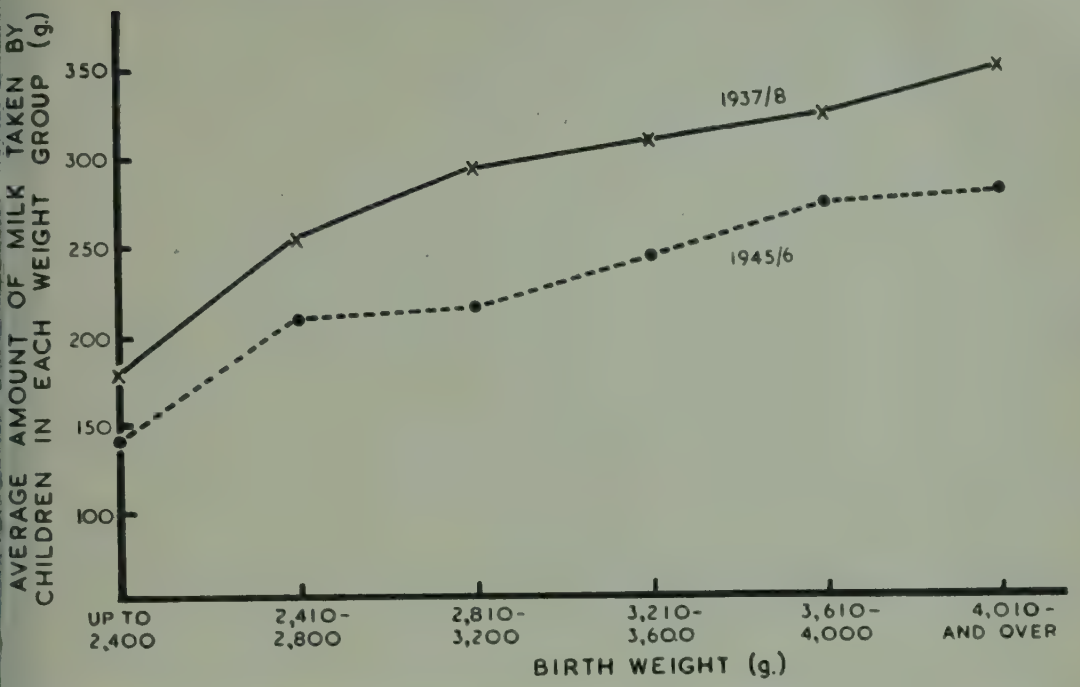

FIG. 11. Relation between birth weight and amount of milk taken on 5th day: 1937/8 and 1945/6.

smaller percentage of larger children and an increased desire to avoid operative interference would both have tended to reduce the proportion of forceps deliveries in the later years, and therefore to decrease the number of children who, as a result of birth trauma, would not feed satisfactorily. In general the children born in 1945–6 appeared to have been of normal vitality and there was no evidence of undue difficulty in inducing them to suck.

In 1937–8 supplementary feeds were given to about 14 per cent of the children on the fifth day after birth, but in 1945–6 they were given to 21 per cent of them. According to the nurses responsible for the feeding, the indications for giving

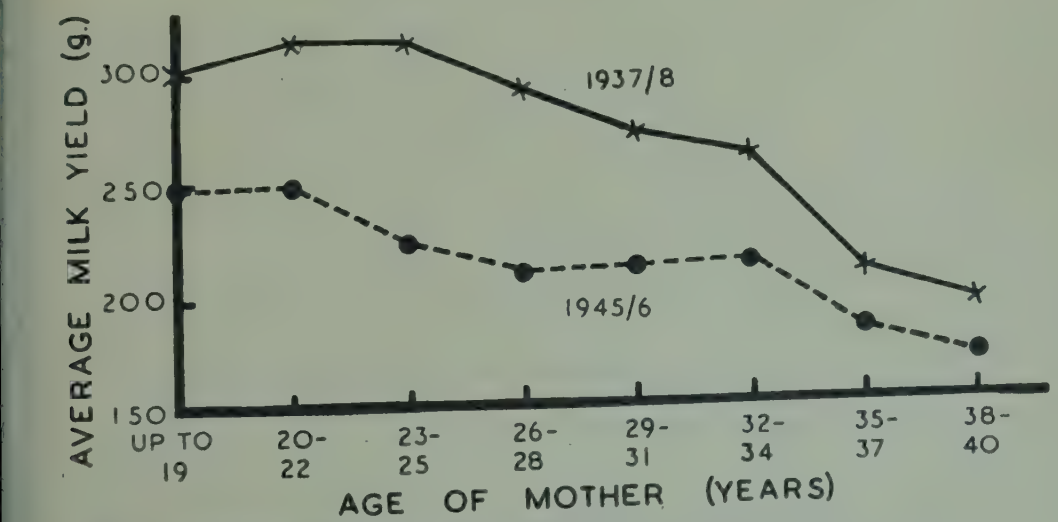

FIG. 12. Relation between the age of the mother and the amount of milk taken by her first child on 5th day: 1937/8 and 1945/6.

the supplements had not changed. If this was so, the more extensive use of the supplements in 1945–6 was another indication that the mothers' supply of milk was then less adequate than in 1937–8.

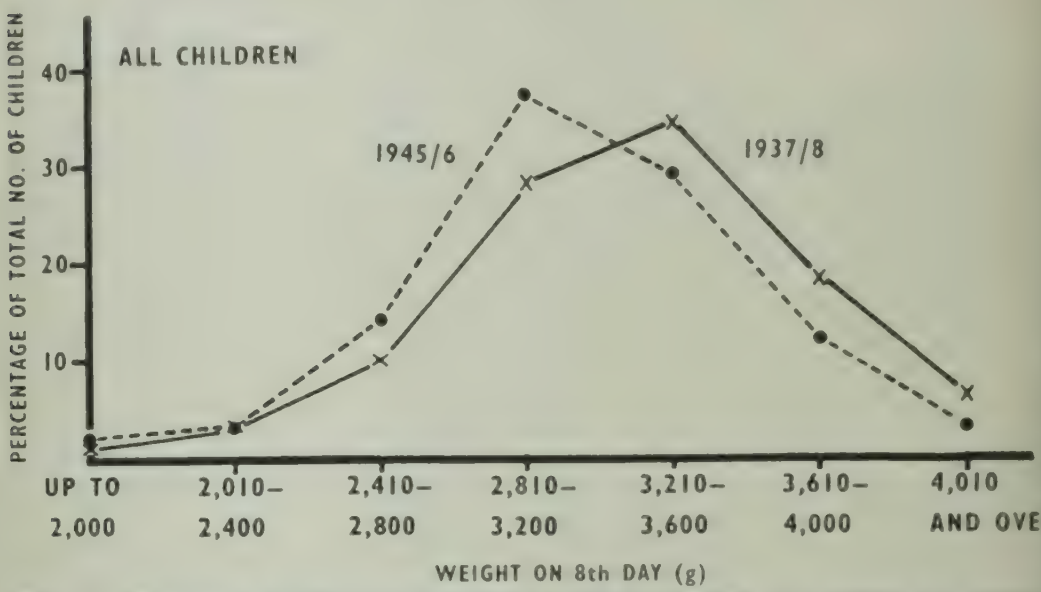

FIG. 13. Frequency distribution of weights of children on 8th day, 1937/8 and 1945/6. Difference of means/S.E. of difference = 11·5.

The combination of low birth weight and reduced milk supply inevitably caused the children of all birth-weight groups to be lighter on the eighth day in 1945–6 than in 1937–8 (Fig. 13). The average weight of all the children of this age in 1937–8 was 3,283 g., and in 1945–6 it was 3,138 g. In neither of the two-year periods, therefore, was the birth weight regained, but the children born in 1937–8 were nearer to it than those born in 1945–6.

TABLE 8

Net loss of weight from birth to 8th day as percentage of birth weight

Birth weight (g.)	Loss as percentage of birth weight	
	1937–8	1945–6
Up to 2,800 ..	1·80	2·90
2,810–3,200 ..	2·45	3·35
3,210–3,600 ..	2·75	4·35
3,610 and upwards	3·40	5·20

In order to differentiate between the effects of low birth weight and reduced milk supply on the weight on the eighth day, the children in both two-year periods have been grouped according to birth weight, and Table 8 shows the percentage loss in each weight group at eight days of age. In both 1937–8 and

1945–6 the children who were largest at birth were the farthest from the birth weights, but the loss was greater among children born in 1945–6 than among those born in 1937–8. It seems therefore that the milk yield of the mother played a greater part in determining the baby's progress than did the weight of the baby at birth.

A comparison of the lactation of mothers in 1937–8 and 1945–6 would be incomplete without some consideration of the mental strain of the later years. Germany was very prosperous in 1937 and 1938, although war must have seemed inevitable. In Wuppertal the prosperity continued and life was not greatly altered until the first big raid in 1943. From then onwards there was much more danger from the air, until by the end of the war a large part of the town was destroyed. The difficulties of ordinary life, particularly in shopping for food, in travel and in housing, gradually accumulated and reached their most serious point in 1945, at the end of the war, and immediately after it. If constant worry could affect lactation, this period would be expected to show its influence most clearly, and would provide the greatest contrast to the pre-war years. It is obviously impossible to assess quantitatively the value of the various mental and emotional stresses in terms of milk production, and perhaps all that can be said definitely is that in 1937–8 the mothers were nearer to that desirable state of mental tranquillity which most authorities consider to favour lactation.

Later Lactation

Information concerning later lactation is confined to about 400 women, or approximately one-third of the total number of mothers who gave birth in the Landesfrauenklinik in the second half of 1946 (see p. 351). No corresponding data for the pre-war years are available. The records that were obtained for partial breast feeding may have been influenced by the desire of the doctors and welfare workers to ensure that the women should receive the extra rations during lactation. Officially, a "test-feed" should have been observed and a satisfactory amount of milk recorded before the extra rations were allowed, but in actual practice this was very seldom done. The records, therefore, will tend to err by overestimating the number of mothers who were partially feeding their children. The records of unsupplemented breast feeding were not so likely to be exaggerated because the women got the same extra rations whether their babies were fully or partially breast fed.

The percentage of mothers able to provide full and partial breast feeding is shown graphically in Fig. 14. Results obtained by Paton and Findlay (1926), who studied Glasgow women living in poor circumstances, are given for comparison. The percentage of women feeding their children without supplements at the end of one month was approximately the same in Glasgow and Wuppertal, and the proportions fell together in the second month. After that the ability of the Wuppertal women declined rapidly, and at six months only 5 per cent were fully feeding their children as compared with 36 per cent of the Glasgow women. The percentage of Wuppertal mothers who were said to provide some breast milk was high, particularly in the first three months. If the Wuppertal figures are correct it appears that 40 per cent of the women were able partially or wholly to breast-feed their children for the first five months; the corresponding figure for Glasgow was 62 per cent.

TABLE 9

Relation of milk yield on the 5th day to average duration of breast feeding, with and without supplements

Milk yield on 5th day (g.)	Multiparous women			Primiparous women			All women		
	No. of women	Months of full breast feeding	Months of breast feeding with supplements	No. of women	Months of full breast feeding	Months of breast feeding with supplements	No. of women	Months of full breast feeding	Months of breast feeding with supplements
0–100	15	1·4	5·4	20	1·0	4·8	35	1·2	5·1
110–200	34	2·0	6·2	73	2·0	6·0	107	2·0	6·1
210–300	79	2·4	6·9	66	2·4	6·8	145	2·4	6·9
310 and more	61	2·4	6·1	43	2·6	6·3	104	2·5	6·2

TABLE 10

Percentage of birth weight gained at the end of 6 months

Months of full breast feeding	0		1		2		3 or more	
	Number of children	Percentage gain	Number of children	Percentage gain	Number of children	Percentage gain	Number of children	Percentage gain
Boys	6	117	10	103	15	107	22	107
Girls	9	106	14	105	7	111	36	108
First children	6	112	11	102	7	111	27	104
Later-born children ..	9	109	13	107	15	107	31	110
All children	15	110	24	104	22	108	58	107

The Wuppertal data confirm the suggestion made by Robinson (1947) that the yield of milk on the fifth day is quantitatively related to the duration of lactation. It will be seen from Table 9 that the greater the amount of milk on the fifth day the longer the women were able to feed their children, with or without supplements.

Multiparous women did not seem to be able to feed their children longer than primiparous women in spite of the fact that they produced more milk during the first eight days. This may have been because, once they got home, the multiparous women shared their extra rations with their other children.

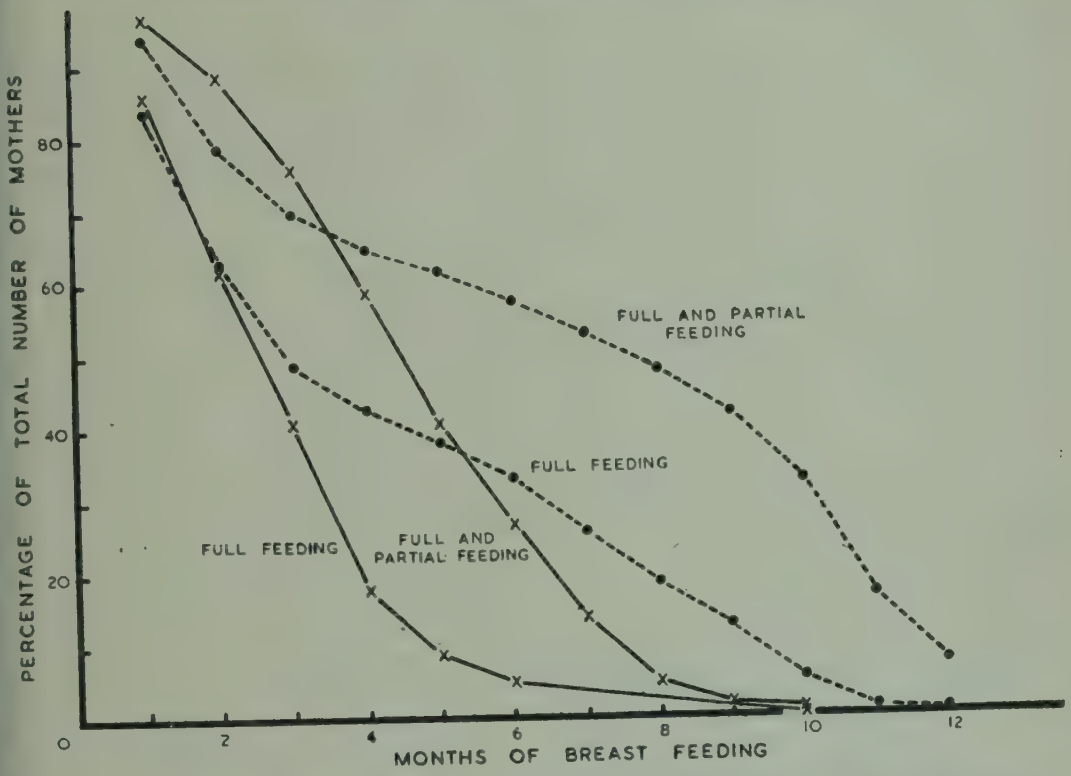

FIG. 14. Percentage of mothers providing full and partial breast feeding in Glasgow (Paton and Findlay, 1926) and Wuppertal, 1946; Glasgow women •------•, Wuppertal women x——x.

The children for whom satisfactory information was available rather more than doubled their birth weights at the end of six months, and the weight gain was independent of the length of time they had been breast fed. Boys and girls appeared to do equally well, as did also first-born and later-born children (Table 10).

DISCUSSION

The evidence brought forward leads to the conclusion that children born in the Landesfrauenklinik in Wuppertal in 1945–6 were certainly lighter at birth and possibly slightly shorter in length than the children born in 1937–8, and that there was coevally a large reduction in the amount of milk the children obtained from their mothers. The fall in birth weight was not sudden and spectacular, except perhaps in the first half of 1945, and the average fall even then (185 g.) was less than has been attributed to undernutrition in other countries; it represented a loss of about 6 per cent of the average weight in 1937. The difference in the

amount of milk taken in 1937 and 1945 was about 80 g. on the fifth day after birth and 90 g. on the ninth day; this represents a reduction of about 25 per cent on the fifth day and 22 per cent on the ninth.

The size at birth and milk yield were at their lowest when the food situation in Wuppertal was at its worst, and improved when more food was obtainable. It has been shown that the populations in 1937–8 and 1945–6 were comparable, and that the slightly shorter time that the children spent *in utero* in 1945–6 was not the main cause of the reductions in weight. The comparisons which have been based on the data of Stander and Pastore (1940) support the theory that the Wuppertal women themselves were in 1945–6 a little below their normal weight at the beginning of pregnancy and at delivery, but the connexion between their own reduced weight and the reduced weight of the children cannot be properly established.

Direct comparisons between the diets of Wuppertal women in 1937–8 and 1945–6 are impossible because no details of the diets before the war are known. Of that time it can only be said that economic conditions were good and choice was free. In 1946 the women were entitled to receive rations which should have provided about 2,400 Calories per day in pregnancy and 3,500 Calories per day during lactation. The latter figure compares favourably with the 3,000 Calories recommended during lactation by the U.S. National Research Council (1945) and the 3,600 Calories suggested by the League of Nations Health Committee (1936). It is doubtful if many of the Wuppertal women ate food providing so much as 3,500 Calories because even in 1946 they were probably unable to obtain the full quantities of rationed food. The diet given the mothers whilst they were in the Landesfrauenklinik in 1946 provided about 2,300 Calories per day and this was probably much nearer the figure for the Calorie consumption of the ordinary women at home. Such a diet would be considered by most authorities inadequate for a lactating woman whose life was other than completely sedentary. The League of Nations Commission estimated the household duties of the women to be the equivalent of eight hours' work and made her an allowance of 600 Calories for this work. The needs of the Wuppertal women, forced to do most of their shopping on foot, and often covering relatively long distances (*McCance and Widdowson*, p. 1), may well have exceeded this estimate.

The Landesfrauenklinik diet contained 75 g. total protein, of which about 25 g. was from animal, and 50 g. from vegetable sources. It is likely that women in 1937 would have eaten more than this amount of protein, and much more animal protein. Miegs (1922) and Smith (1944), reviewing reports of the experimental feeding of domestic animals, came to the conclusion that increase and decrease of protein in the diet led to increase and decrease in the milk yield, and Deem (1931) found that increasing the protein in the diet from 90 to about 145 g. per day caused the large increase of about 110 c.c. in the daily milk yield of four out of five women. Her results are really in keeping with those of other workers who have found that women receiving "good" diets tend to give more milk than those receiving diets classed as "poor", because generally the "goodness" or "badness" of a diet has been judged in the past very largely by the amount of protein, and especially animal protein, it contained. It is worth noting in this connexion that the supplementary food given by Ebbs, Tisdall and Scott (1941) and believed to be so beneficial, particularly to lactation, added 45 g. protein to diets containing only 56 g. protein, and of the 45 g. more than 40 g. was of animal origin. In diets more or less freely chosen, protein intakes tend

run with Calories, as Widdowson (1947) has demonstrated for children and Cameron and Graham (1944) for pregnant women. In Wuppertal in 1945–6 a demand for extra Calories would have been met most easily by eating potatoes. These contain only about 2·0 per cent protein and large quantities would have been needed to increase appreciably the protein intake; bread, with about 8 per cent protein, would have been more satisfactory but was apparently less frequently obtained (see p. 353). It must be admitted that to ascribe the reduction in birth weight, and more especially in milk yield, to a relative or absolute reduction in protein eaten by the Wuppertal women would be conjectural, although the daily allowance of 100 g. total protein, which seems usually to be considered necessary for the pregnant and lactating woman, could seldom have been obtained. The Wuppertal diet contained very little fat, but human requirements of fats are unknown, and their importance in nutrition, apart from their functions as vehicles for the fat-soluble vitamins, is unsettled. Milk fat is derived in part from fats and fatty acids circulating in the bloodstream, but there are probably other sources (Folley and French, 1950), and the extent to which human milk production depends on one or other of the raw materials is unknown. The desire for fat, which was so clearly shown by the answers of the women when questioned about extra food, was largely dictated by habit and the undoubted value of fat in increasing the palatability of foods, especially in cooking. There is no evidence that it represented a physiological need, although the total amount of fat obtained was certainly much less than the amount normally consumed in peace time.

There is no doubt that pregnancy and lactation make heavy demands on the mineral resources of the mother, and it is not unusual for lactating women to be in negative calcium balance, although the balance is very easily improved by vitamin D (Garry and Wood, 1946). No cases of osteomalacia or osteoporosis were found among the adult population in Wuppertal, although it is difficult to see how a positive calcium balance could have been maintained (*Widdowson and Thrussell*, p. 296); no increase in infantile rickets was reported by the Landesfrauenklinik doctors amongst the 1945–6 babies, and skeletal development appeared to be normal, since the size of the skeleton, judged by length at birth, was little altered despite the changes in weight. Nevertheless the stores of calcium possessed at delivery by the Wuppertal women may have been lower than normal, and the reduction may have had an effect on lactation. This also is conjecture, but some writers (e.g. Liu, Su, Wang and Chang, 1937) have maintained that calcium salts, if added to the diet of lactating women who are also receiving vitamin D, will increase the milk yield. The cow has a safety mechanism in that the amount of milk can be reduced if the loss of minerals becomes dangerous (Schmidt and Greenberg, 1935), but the mechanism sometimes breaks down and death may then ensue. It is within the bounds of possibility that the lactation failures observed in Wuppertal may have been connected with the depletion of the calcium stores of the mothers. Very few of them had access to large supplies of preformed vitamin D, but the natural formation of that vitamin through the action of sunlight was presumably unchanged.

There can be little doubt that the fluctuations in size at birth and milk yield were associated with variations in nutritional status, but it would be unwise to claim that nutrition alone was responsible. So far as is known, the growth of a child within its mother is not directly affected by her mental cares, but the nutritional status of the Wuppertal women was to a large extent dependent

upon her own initiative and self-sufficiency. If she was enterprising she would by some means or other get extra food. In this indirect way, therefore, her mental outlook might have affected the development of her unborn child.

Lactation offers a contrast to pre-natal development in that emotional and other disturbances are known to be directly prejudicial to success. It may well be that the failure of the Wuppertal women to lactate in 1945–6, although it was due partly to the physical factor that gave them small children, was also the result of their mental condition. They left hospital earlier than women delivered in 1937–8 and when they got home they must have had added problems and anxieties. All the circumstances were against successful lactation, at least if we agree with Budin (1897) that: "Les chagrins, les émotions morales, sont de nature à troubler la sécrétion lactée". Exactly how the mental reaction of a woman to her circumstances affects the nervous or hormonal mechanisms which determine the flow of milk is still unknown. Undernutrition and anxiety usually occur together and we cannot say which is the more important.

SUMMARY

1. An analysis has been made of the records of 22,000 births at the Landesfrauenklinik, Wuppertal, during the years 1937 to 1948.

2. The average birth weight was lowest in 1945, when it was 185 g. less than in 1937. 1945 was probably the year in which there was the greatest shortage of food.

3. A very small reduction in length accompanied the reduction in weight.

4. The period of gestation was slightly shortened but not enough to account for the reduction in weight.

5. The children took considerably less breast milk in 1945–6 than in 1937–8.

6. It has been concluded that the state of nutrition of the mother must have played some part in the production of the changes. Anxiety may have contributed to the failure of lactation.

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XXIX. THE VOLUME AND COMPOSITION OF HUMAN MILK

by Mavis Gunther and Jean E. Stanier

INTRODUCTION

One of the earliest scientific accounts of breast feeding among severely undernourished women was made during the siege of Paris. Descaine (1871) did not describe the women's food, but contemporary records leave no doubt about the scarcity at that time. Descaine found that out of 43 women who were attempting to feed their children from the breast, 16 women (aged 25–32) had insufficient milk and three-quarters (presumably 12) of their babies died of hunger; 12 of the others, (aged 21–28) had enough milk, but the baby was gaining weight at the expense of the mother. Descaine stated that insufficient food always reduced the amounts of butter, casein, sugar and salts in milk, and that its composition was restored to normal after four or five days of "alimentation reparatrice". Schukowski (1871) estimated the fat in milk from mothers on admission to a foundling home in Moscow and after a period of residence there. The percentage of fat in their milk rose from 1·8–3·0 on admission to 3·2–4·0 later. He also estimated the amount of fat in milk secreted during a fast and found a rise from 0·88 to 3·4 per cent. Neither Descaine nor Schukowski described how his samples were taken.

In 1900 Schlossmann noted that some wet-nurses in an institution temporarily lost their milk when they did not eat the food provided, but recovered their output when they were given a more congenial diet.

The hungry period during the 1914–18 war and in the succeeding years produced a spate of papers from Germany on the effect of undernutrition on lactation, and in some instances one suspects that political rather than scientific reasons may have prompted their writers. Declarations that there was no effect, which were reassuring during the war, gave place after the armistice, when the country was in submission and when, indeed, conditions were worse, to expressions of the contrary belief. Thus Steinhardt (1917) studied the duration of lactation at a Nürnberg clinic before the war and again in 1916. He concluded that in 1916 slightly fewer women were feeding their babies from the breast for more than six months; but he also found that of 85 women who had fed one child before the war and one after the war had broken out, two-thirds were feeding their babies for longer in wartime. Grumme (1917) pointed out that a greater desire to feed from the breast could account for some of Steinhardt's findings, and that in 1916 food was still relatively easily to obtain. He also drew attention to the likelihood that mothers would be able to feed their second babies from the breast for longer than they could their first. In a further article, Grumme (1920) in Fohrde made the theoretical estimate that some mothers in Germany who were receiving about 45 g. of protein a day were secreting 20–25 g. in their milk. He concluded that shortage of protein was the reason for failure of lactation after one month among 3 of his patients, who had previously fed their children successfully.

Momm and Kraemer (1917, 1919) rejoiced to find that the milk secreted by poor mothers in Freiburg was unaltered in composition in spite of the blockade. Between the 2nd and 22nd weeks of lactation samples of milk, taken sometimes from the whole day's secretion and sometimes from samples of fore- and hind-milk, contained 3·61 and 3·71 per cent of fat in 1917 and 1919 respectively, and

these values were compared with the percentage of 3·74 found by the authors before the war. In a third paper, however, Momm (1920) concluded with bitterness that the proportion of women fully breast-feeding on the tenth day had decreased during the war. Martin (1920) of Elberfeld attributed Momm's findings to faulty technique, saying that out of 1,000 women under his (very strict) régime only 8 had been unable to feed their babies on the tenth day. Since Martin's cases were delivered in their homes and since artificial feeding was not allowed, his criterion of failure of lactation may have been different from that of others. Deleterious effects of war diet were implied, with little or no evidence, in four other articles. Kaupe (1918) noticed that babies in Bonn had not been gaining weight so well. Klotz (1920), working in Lübeck, considered that the percentage of fat in breast milk was below normal in 2 mothers whose babies were gaining weight more slowly than was expected from the volume of milk taken; he found 3·0 and 2·5 per cent of fat in 24-hour samples taken between the 20th and 25th days. Lederer (1921) concluded that the percentage of fat (estimated from single samples) was lower in the milk of some women in Vienna whose babies were not thriving than in the milk of others whose babies were. Hammann (1921) considered that the wet-nurses, usually eight in number, in a Berlin home gave less milk per day from 1917–20 than they had given before. Bergmann (1919), whose evidence was more complete, gave records of the weight curves of her children, a son born in 1915 and a daughter born in 1917, and of the volumes of milk taken by them. The birth weights were virtually the same; the initial weight loss of the second child was greater, but if allowance is made for this, the weight curves can almost be superimposed. The first child was constipated, the second was not. Since the second child consistently took more milk, Bergmann concluded that her milk in the second lactation had a lower Calorie value which she attributed to her small protein intake. In contrast to the above findings, figures suggesting that the war diet had not impaired the mothers' ability to lactate were given by Hotzen (1919). Mothers attending a clinic at Magdeburg were found to be nursing for longer in 1918 than in 1913, and babies were gaining on average more weight per day. Pasch (1921) considered, on the basis of tests made on samples of fore- and hind-milk, that the percentage of fat in the milk of 5 Leipzig women on poor diets was normal.

The 1939–45 war has yielded further accounts of lactation in times of acute food shortage in France, Russia, Finland and Holland. Lavagne and Mathieu (1943) analysed mixtures of breast milk withdrawn in the morning, at midday and in the evening from 34 women in Versailles. They expressed their results as the number of women in whose milk the percentage of fat or other milk constituent was above, equal to, or below the standard set out by Marfan (1920). Although there were as many women with percentages of fat above as below the chosen standard, the authors believed that the Calorie value of the milk was unusually low on account of the low percentage of lactose which was found in all but one sample. The observations made by Antonov (1947) during the siege of Leningrad confirmed his earlier ones, made in 1918, that so long as the mammary gland received sufficient physiological stimulation, milk continued to be secreted in spite of starvation, although the quantity might be reduced and the length of lactation shortened. In Helsinki, Salmi (1944) analysed the milk brought to a milk bank by 68 women in 1939 and compared it with that brought by 130 women in 1941–2. His methods of sampling are not clear, for although he mentions taking the whole day's milk, many of the donors

were probably also feeding their own children. In 1939 the percentage of fat in the milk from individual donors ranged from 1·9 to 9·6, a greater range than is usually found in 24-hour samples. Salmi found that the average percentage of fat in the donors' milk had fallen from 4·1 in 1939 to 3·1 in 1941–3. As von Sydow (1945) of Gothenburg has pointed out, the diversity in the methods of obtaining milk practised by donors to a milk bank is so great that Salmi's differences could have been brought about by changing customs. Even so, the number of analyses made by Salmi commands a certain respect. Von Sydow estimated the amount of fat in the milk of 10 Polish women in May 1945 on their arrival from Ravensbrück concentration camp. Nine of the samples, obtained by emptying the breast completely at 2 p.m., contained more than 4 per cent of fat, and two months later two of them contained 5 per cent. Von Sydow's comment was that although racial differences might account for the high percentage of fat in the milk of the Polish women, the figures did not support Salmi's conclusion that undernourishment lowered the nutritive value of milk. Von Sydow does not appear to have considered the possibility that his high percentages of fat were due to the time of day at which the samples were withdrawn.

In the Dutch famine (1944–5) the proportion of mothers feeding their babies from the breast was about the same as it had been in the same months a year before (Smith, 1947), and Jonxis is stated by Smith to have found no significant deviation from the normal in the composition of the milk at that time. It is possible that the women made greater efforts to suckle their children during the famine because there was little chance of feeding them in any other way.

Kon and Mawson (1950) assayed the vitamins in over 2,000 samples of milk from a country town (Reading) and a city district (Shoreditch) between 1941 and 1945. They studied the effect on the composition of milk of such variables as time of day, stage of lactation, milk yield, and age and parity of the mother. They found similar concentrations of vitamins in the milk taken in the two areas, but there was a smaller percentage of fat in the samples of milk from the women of Shoreditch. The samples were obtained by emptying the breast once in the morning. The milking technique was standardized as much as possible, but the collectors in Reading and Shoreditch were not the same, and the authors conclude that variations in sampling technique rather than diet may have led to the differences in composition. A small survey of milk taken from Glasgow women who were said to be undernourished was also carried out. The percentages of vitamins in the samples taken there resembled those in Shoreditch, but the difficulty that was experienced in finding women in Glasgow capable of giving a sample in the fourth and fifth weeks of lactation suggested that quantity rather than quality was primarily affected by undernutrition.

A number of investigations into the effect of diet on secretion of milk have been made by experimental alteration of the mothers' diet. Two early investigators, Zaleski (1888) and Pletzer (1899), taking single samples of milk from mothers, found more fat after increasing the protein in the mothers' diet for one to four days. Then came two complementary investigations made by Moll (1908) and Engel (1910). Moll gave a wet-nurse a high-fat diet for ten days between two periods in which she was on a diet containing little fat. He estimated the amount of fat in aliquots of fore- and hind-milk withdrawn in the morning and the evening, and his eight-day averages obtained by this ineffectual sampling suggested that the milk contained more fat when the wet-nurse was taking extra fat. Engel, however, believed that extra fat in the diet could not increase the

percentage of fat in the milk of normal women, although he thought that reducing the dietary fat could decrease it; he ascribed Moll's results to this effect. Engel himself reduced the fat in the diet of a wet-nurse and, on the basis of three samples, reported a decrease in the percentage of fat in her milk at this time. The amounts of fat in the diets of these two wet-nurses were not stated. At about the same time Plauchu and Rendu (1911) reported that dietary supplements of 50 g. of butter had no effect on the percentage of fat in 10 c.c. samples of fore-milk.

Subsequent workers have used more elaborate techniques with basal diets of known Calorie value. Kleiner, Tritsch and Graves (1928) investigated four groups of newly delivered women who all received 270 g. of carbohydrate, 50 g. of protein and 150 g. of fat daily, providing a total of 2,600 Calories. There were from 17 to 31 mothers in each of the four groups. One group was given in addition 60 g. of rice, one the same amount of tapioca and one 100 g. of cream containing 40 per cent fat. The fourth received no supplement. Milk for analysis was withdrawn at 9 a.m. on the fifth and ninth days *post partum* and the amount of milk taken by each baby was measured by weighing before and after one feed on the seventh day. The percentages of protein and fat in the milk were similar in all four groups, but the average amount of milk taken at the test feeding suggested that the mothers receiving the carbohydrate supplements gave the most milk. The babies in each group gained similar amounts of weight.

A more thorough study was made by Deem (1931b) of five mothers over a period of seven weeks. The women were in established lactation, secreting 0·5 to 1·5 litres a day, and, being very active, they consumed diets with values ranging from 2,899 to 4,313 Calories per day. The percentages of fat and protein were estimated in the milk obtained from one breast in 24 hours at the end of each seven-day dietary period. The lowest intake of protein was 61, the highest 147 g. daily, while the fat varied between 85 and 251 g. Throughout the experimental period the percentage of fat in the milk tended to rise. Although the author concludes that the diet containing much fat had increased the percentage of fat in the milk, and that the high-protein diet had increased the volume of milk secreted, the variations in the reported figures make the validity of the conclusions doubtful. A somewhat similar experiment was conducted by Ruzicic (1934) on 5 wet-nurses. Here the women either had a normal mixed diet or a diet consisting entirely of meat, bread or butter or two of these together. The difference in the composition of the diets was therefore great, and there were days when the women ate, for instance, nothing but 450 g. of butter. Ruzicic found that the volume of milk secreted was reduced by all but the mixed diet. The most interesting observation was that the percentage of fat in the milk of two of the women was increased by very large supplements of fat and also by starvation, and that the volume decreased in both circumstances.

Besides these studies there have been two in which only the volume of milk secreted has been measured. A doctor's wife wishing to regain her figure undertook a Banting cure (Keller, 1910). From the time when her child was 5 weeks old she lived for 16 days on 400 g. of meat with two rolls and a little vegetable each day. In this time she lost 2·3 kg. of body weight, and the volume of milk secreted rose slightly, but remained of the order of one pint a day. Adair (1925) found that the amount of milk taken by 400 babies in four groups was the same whether the mothers received a diet high in protein, fat or carbohydrate or a balanced diet; details of the mothers' diets or babies' weights were not specified.

A comparison of the proportions of women breast feeding among groups receiving supplemented and unsupplemented diets was made by Ebbs, Scott, Tisdall, Moyle and Bell in Toronto (1942). Eighty-six per cent of the mothers who had received the impressive supplement of 1½ pints of milk, an egg, 200 International Units of vitamin D and some wheat-germ daily, and also 2 lb. canned tomatoes, ½ lb. cheese and 7 oranges a week, were still feeding their babies from the breast six weeks *post partum*. The diets of the other two groups, one with low incomes, the other with sufficient money per head in the family to buy a very good mixed diet, were unsupplemented, and 59 and 71 per cent respectively of the women in them were feeding from the breast at the sixth week.

Finally, three investigations have centred on the influence of specific dietary fats on the composition of the milk fats. Thiemich (1899) and Engel (1906b) came to opposite conclusions when investigating whether the iodine number of milk fat could be shifted by giving the mother oils of different iodine values. Bendix (1898) found bound iodine in the milk fat of a woman who had eaten 239 g. of iodized sesame oil in five days. He concluded that, although others believed that rich diet did not increase the fat of the milk, a proportion of that fat is derived from dietary fat.

TABLE 1

Composition of the official rations for the pregnant and lactating woman and the normal consumer, Wuppertal, September-October, 1946

Foodstuff	Allowance (g./day)		
	Pregnant woman	Lactating woman	Normal consumer
Bread ..	445	516	354
Cereals ..	89	125	45
Infant's food	9	18	—
Meat	30	30	16
Fish	21	21	21
Fats	25	43	7
Sugar	27	54	9
Jam	32	48	16
Cheese ..	2	2	2
Full milk ..	500	1,250	—
Skimmed milk	125	125	125
Artificial coffee	9	9	4
Potatoes ..	430	430	285
Vegetables ..	71	143	71
Total Calories	2,425	3,426	1,409

PRESENT INVESTIGATION

The Dietary Situation in Wuppertal

The investigations in Wuppertal were mostly made between September 1946 and May 1947, and during that time the official rations for normal consumers provided about 1,400–1,500 Calories per day and they had been as low or lower for the previous six months (*McCance and Widdowson*, p. 1). Even these rations were not always obtainable. Bread and cereals were particularly difficult at times, but vegetables were relatively abundant for those with gardens, especially during the autumn. Pregnant and nursing women were entitled to supplementary rations, and these are shown in Table 1. One mother in this

investigation, who secreted a very large volume of milk (1,600 c.c. per day), was acting as a wet-nurse and was receiving extra rations under three scales of allowance. Besides the ordinary lactating woman's ration, she received the special supplement for wet-nurses, and also a bonus given for producing more than 12 litres of milk per month. She was thus entitled to about 8,000 Calories per day. It must, however, have been difficult for some of these women to obtain their rations when food was short, since prolonged queuing at unusual times, frequently at places some distance from home, was often essential for success. Furthermore, rations were as a rule divided out among the household, and it is most improbable that any pregnant or nursing woman with a husband and children ate all the rations to which she was entitled.

The Problems of Sampling

It is now clear that nearly all the older work relating to fat was vitiated by the way in which the samples of milk were collected. The principal difficulty in sampling comes from the fact that hind-milk is richer in fat than fore-milk. This fact was known to Thomas Young in 1761 and had probably been part of traditional lore. At any rate, Young complained that the variability of fat from time to time made the sampling of milk difficult. Parmentier and Deyeux (1790) who, like Young, relied simply upon naked-eye observation, confirmed the richness of hind-milk, not only of cows and humans, but also of goats, sheep, mares and asses. In the first chemical estimations of fat in milk, made by Peligot (1836), the successive samplings from one milking were shown clearly to be increasingly rich in butterfat. It is remarkable that, in spite of the clarity of this early work, the importance of emptying the gland completely when sampling the milk for fat has been ignored countless times and re-discovered by several workers. Various attempts have been made to estimate the fat in the milk by taking aliquots of fore- and hind-milk while allowing the baby to take the intermediate fraction. This method, first put forward by Reyher (1905), was immediately shown by Freund (1905) and Engel (1906a) to be unsatisfactory, since the percentage of fat does not necessarily rise by equal increments with the withdrawal of equal volumes. The amount of fat in a sample taken after the baby has had half its customary time at the breast has been shown to be no measure of the percentage of fat in the whole volume of milk removable from the same gland.

Superimposed on these difficulties is the problem of deciding when the gland has been completely emptied. The yield of a cow, that is the volume of milk which can be obtained from the udder, may be reduced by some disturbance of the "let-down" process, by delaying the milking after the "let-down" has taken place, or by slow milking (Miller and Petersen, 1940), or it may be increased by as much as one third after intravenous injection of pituitary oxytocic principle. The "let-down" process in cows, and its simulation and exaggeration by injection of oxytocic principle, have their counterparts in human lactation. A woman who is frightened, or unaccustomed to artificial methods of emptying the breast, might be expected for these reasons alone to yield less hind-milk, and the resulting low percentage of fat in her milk would be wrongly interpreted. Differences in the percentage of fat have been ascribed by Widdows and Lowenfeld (1933) to removing the milk by hand or by pump, but their results could also be explained by inequality of the "draught" action (the equivalent in humans to the "let-down" in cows) in the emptying of the first and second breasts. In addition to the problems produced by the difficulty of emptying

the breast, there are others due to incomplete milking at the previous time. Davidson (1924) and Shaw (1942) have shown that this residual milk contributes to the milk of the next milking. Although Davidson's and Shaw's investigations were made on cows there is no reason to doubt the applicability of their findings to humans. It is important, therefore, to empty the breast before starting any experimental period if the percentage of fat is being studied, and it follows that successive milkings from one breast are of greater value than single ones.

The percentage of fat in breast milk varies during the day (Plauchu and Rendu, 1911; Deem, 1931a; Nims, Macy, Brown and Hunscher, 1932; Gunther and Stanier, 1949) and the highest value, usually found about midday, may be almost twice that of the lowest. If comparisons of fat content are to have any value it is believed that samples of all the milk secreted by one breast throughout 24 hours should be taken, and, if single samples only have been taken, the figures should be interpreted according to the time of day. The length of the interval between times of milking has been held to influence the percentage of fat in the milk of both cows and humans (Peligot, 1836; Reiset, 1849). Once again the evidence is complicated by side effects, for varying the time of milking modifies the conditioned reflexes of the "let-down" in the cow. This effect, together with the effects of diurnal variation and the duration of milking time, renders uncertain the conclusions of some workers, but it appears from investigations by Ruzicic and Popovic (1939) and Gunther and Stanier (unpublished) that varying the intervals between times of milking from two to eight hours has little effect on the percentage of fat in the total milk secreted by the human breast.

A further factor which affects the percentage of fat in human milk is the stage of lactation (Nims, Macy, Hunscher and Brown, 1932), but the phases during which the percentage of fat is high may not be the same in all women.

The percentage of protein varies more definitely and consistently with the stage of lactation than does that of fat. It falls throughout lactation, but much more rapidly in the first ten days than in later stages (Kon and Mawson, 1950).

Methods

The methods of analysing chemical constituents, with the exception of calcium, were those used by Kon and Mawson (1950), and had been practised by one of the present authors in their laboratory in Reading; calcium was estimated as described in the Appendix to this Report (p. 401). The fluorimeter used for the measurement of concentrations of aneurin and riboflavin was of the Cohen type, and similar in principle to that used in Reading. The concentration of vitamin A was measured by use of a photoelectric absorptiometer, and not with the photoelectric spectrophotometer used in Reading. Both instruments, however, came from the Reading laboratory and were checked for agreement with the instruments used in Kon and Mawson's investigation.

THE COMPOSITION OF BREAST MILK

Women in Established Lactation

Subjects and Samples

This part of the investigation was made between September and December 1946. An attempt was made at first to select the most undernourished mothers on the basis of their height and weight when they were discharged from the Landesfrauenklinik in Wuppertal. However, it was found that, for various reasons, very few of the selected women were either feeding their babies without supplements three weeks after delivery, or were willing to give a sample. Much

time was wasted in visiting unsuitable cases, and after 12 samples had been collected, an arrangement was made by which the German Health Visitors, who knew how the women in their own districts were lactating, requested certain ones to be at home to give a sample at a definite time. The Health Visitors were asked to select mothers whom they considered undernourished, but since the number of mothers willing and able to give samples was so small it is unlikely that much choice was possible. It should here be emphasized that the women selected were inevitably those who were lactating fairly successfully, and that the most undernourished women may or may not have been included. Most of the mothers who were visited lived in one or two rooms, and in poor surroundings; many had been bombed out or were evacuees, and one was a refugee living in a bunker. Of the 61 mothers visited, 20 were primiparae and 41 multiparae.

Some information was obtained about each woman's diet, and an attempt was made to discover whether she had obtained more or less than the official ration for pregnant and nursing women, how much of it she gave to the rest of the family, how many people fed together in the same house, whether the mother possessed or had access to a vegetable garden, and so on. This information was obtained with a variable degree of success. The opinion was formed that a few of the women were certainly undernourished. Twenty-four of the 61 mothers visited had vegetable gardens, and about half had had vitamin tablets irregularly during pregnancy and lactation.

The mothers were asked to feed the baby early in the day, and then either not to feed it again until they were visited between 10 a.m. and 12 noon, or to feed it from one breast only, keeping the other for the sample. It was hoped in this way to be able to empty a breast which had last been emptied four to six hours previously. However, this was not always possible, for the times at which the mothers fed their babies varied very much. Moreover, some mothers gave one breast, but others both breasts, at each feed, and quite often samples were taken from breasts which had not been given to the baby since the previous evening. A further uncertainty was introduced by the fact that at the first feed of the day the baby might not have emptied the breast which it was proposed to empty between 10 a.m. and noon. This indeed was probable if the women were producing large volumes of milk. No sample was taken if it was found that a woman had quite recently fed her baby from both breasts. Other mothers were rejected because they were giving a large supplement with each feed, or to replace one feed. Samples were taken from 12 mothers who were giving small supplements, but who were still nursing their babies five times a day.

The breast was emptied by manual expression. About 30 c.c. of milk were required for all the analyses, and if the mother wished it, any milk over and above this quantity was returned to her after the breast had been emptied. The mothers were on the whole co-operative and willing to give a sample so long as they had enough milk and did not feel that the baby was being robbed.

Samples were taken from women in the 3rd to the 28th weeks of lactation, but most of the samples were taken before the end of the 13th week, for after this few mothers were feeding their babies without large supplements.

Results

The volumes of the samples obtained ranged from 20 to 135 c.c.

Total nitrogen. The figures are given in Table 2 and the values found during the investigation at Reading have been added for comparison. Since the total

nitrogen in milk decreases during lactation the data have been arranged accordingly. It can be seen that the German and English women had similar concentrations of total nitrogen in their milk.

TABLE 2

*Total nitrogen in the milk of women in Wuppertal and Reading**

Wuppertal				Reading 1941–3			
		Total N				Total N	
Week of lactation	No. of samples	Mean (mg./ 100 c.c.)	S.D.	Week of lactation	No. of samples	Mean (mg./ 100 c.c.)	S.D.
3rd– 4th	6	227	27	3rd	5	230	41
				4th	7	211	19
5th– 8th	16	188	19	5th– 8th	63	209	25
9th–28th	11	186	28	9th–12th	115	196	39
				13th–16th	124	191	25
				17th–20th	68	185	23
				21st–24th	33	186	28

* Kon and Mawson (1950).

Fat. For the reasons already discussed no great value can be assigned in this investigation to the figures obtained by the analysis of fat in single samples of milk, and the same is probably true of the English investigation. The amount of fat in the 60 samples of milk analysed in Germany averaged 3·36 g. per 100 c.c. The 32 samples taken 4–6 hours after the breast had last been emptied contained an average of 3·59 g. (S.D. 1·24). Comparable figures at Reading (612 samples) were 4·78 (S.D. 1·47) and at Shoreditch (129 samples) 3·91 g. per 100 c.c. (S.D. 1·42). The milk obtained in Germany appeared on the whole to contain less fat than that obtained in England but whether this was due to undernutrition, sampling or racial differences it is impossible to say.

Aneurin. Table 3 shows the average amounts of aneurin, riboflavin, ascorbic acid and vitamin A found in the milk of the women in Wuppertal and the figures obtained by Kon and Mawson at Reading and Shoreditch have been added for comparison.

The concentration of total aneurin in human milk has been shown by Kendall (1942), Slater and Rial (1942) and later workers to increase in the early stages of lactation and, according to Kon and Mawson, a stable value is reached in the fifth week. For this reason, only values for the fifth week and later have been included in the average. This average, 19·4 μg. per 100 c.c., is somewhat higher than that of 18·3 μg. per 100 c.c. found by Kon and Mawson in England in 1944–5 when the National wheatmeal loaf was being eaten, and much higher than that of 14·7 μg. per 100 c.c. found by them in 1941–2 when white bread was available. Macy (1949) obtained an even lower average (14·2) for the mature milk of American women. It is therefore likely that the high values found in Germany were due, at any rate in part, to the brown bread eaten there.

Low values (9 and 10 μg. per 100 c.c.) were found in milk from two women, and further samples again gave low results. The first woman was in the ninth week of lactation, and her baby was gaining about 180 g. per week. She had started to give a supplement when she was revisited in the eleventh week. She

TABLE

Concentrations of vitamins in the milk of women

Vitamin	Wuppertal			
	Period	No. of samples	Mean value	S.D.
Total aneurin (μg./100 c.c.) (5th–28th week)	1946–7	37	19·4	4·4
Riboflavin (μg./100 c.c.) ..	1946–7	52	21·4	7·0
Ascorbic acid (mg./100 c.c.) ..	1946–7 Sept.–Oct.	45	4·3	0·86
	1946–7 Dec.	9	3·2	0·61
	1946–7 Feb.†	17	3·7	0·70
Vitamin A* (I.U./g. fat) ..	1946–7	47	39·7	14·1

*The concentration of vitamin A in the fat of milk from English women was found by Kon was reached. Therefore for purposes of comparison they corrected all their values for weeks of average weekly values, (formula fitted by Dr. J. O. Irwin, given by Kon and Mawson, 1950). assumed to take place, and the same correction has been applied to the

†Samples taken between 1st and 4th weeks of lactation.

had a vegetable garden, and appeared well-nourished; there were two other children. There was no obvious explanation of the low values. The second woman was in the eleventh week of lactation, and had very little milk. The baby was receiving supplementary feeds, and was gaining about 100 g. per week. The mother was underweight, and said that she had been unable to obtain her full rations either before or after the birth of the baby.

It has been shown by Roderuck, Williams and Macy (1945) and by others that the proportion of aneurin in the free form increases during lactation. Results for the free vitamin were therefore grouped according to the stage of lactation, and, though the numbers in each group were small, the expected trend was found (Table 4).

TABLE 4

Increase in the percentage of aneurin in the milk in the later weeks of lactation

Week of lactation	Free aneurin			Total aneurin			
	No. of samples	Mean value (μg./100 c.c.)	S.D.	No. of samples	Mean value (μg./100 c.c.)	S.D.	Percentage in free form
3rd–4th	4	1·4	—	7	17·3	3·0	8
5th–8th	15	2·4	0·8	37	19·4	4·4	12
9th–28th	10	4·3	2·9				22

Riboflavin. The mean value of 21·4 μg. per 100 c.c. is slightly lower than that found for the milk of women living in Reading or Shoreditch, and much lower than the average of 37·3 given by Macy (1949) for American women. Kon and Mawson, however, showed that the amount of riboflavin in women's milk might be changed rapidly by a meal, particularly if the breast had been emptied

3

living in Wuppertal, Reading and Shoreditch

Reading				Shoreditch			
Period	No. of samples	Mean value	S.D.	Period	No. of samples	Mean value	S.D.
1944–5	191	18·3	3·4	1944–5	104	18·3	2·9
1942–5	616	25·5	7·0	1942–5	136	23·4	5·9
1944–5 Sept.	21	4·0	1·08	1944–5	69	3·3	1·31
1944–5 Oct.	41	3·9	1·21				
1944–5 Dec.	36	3·2	1·33				
1944–5 Feb.	25	3·7	1·37				
1941–5	1,032	31·9	9·8	1941–5	358	32·5	12·4

and Mawson to decrease with advance in lactation until the 17th week, when a constant value earlier than this by reducing them to a 17th week base line by use of a formula fitting a curve A similar decrease in vitamin A concentration in the fat of milk from German women has been values found, so that they may be compared with the English figures.

shortly before it. Their averages for riboflavin, therefore, were calculated only from those figures obtained by the analysis of samples taken during the morning from breasts last emptied between 6 and 7 a.m. When the German figures to be averaged were limited in a similar way a mean value of 23·1 μg. per 100 c.c. (S.D. 4·55) was obtained. This was similar to the Shoreditch figure but the mean of 13 samples obtained during the morning from breasts emptied by the baby after 7 a.m. was almost the same (Table 5).

Ascorbic acid. The difference between the autumn figure of 4·3 mg. per 100 c.c. and the December figure of 3·2 mg. per 100 c.c. is significant statistically, and can be explained by the relative scarcity of vegetables in December. The February figure is not strictly comparable, because it is an average of some samples taken at the Landesfrauenklinik during the early weeks of lactation,

TABLE 5

Effect of time at which the breast was last emptied on the concentration of riboflavin in milk taken during the morning

Time at which breast was last emptied	No. of samples	Riboflavin (μg./100 c.c.)	S.D.
Before midnight, or between midnight and 6·0 a.m.	21	18·8	5·44
Between 6.0 and 7.0 a.m.	15	23·1	4·55
Later than 7·0 a.m. ..	13	25·1	8·20

and it is uncertain whether or not the concentration of ascorbic acid in human milk changes as lactation proceeds. The women in the Landesfrauenklinik, moreover, were probably eating more vegetables than they would have been able to do at home. The mean values and the seasonal trends are similar to those found by Kon and Mawson in Reading. The present results show that the German

mothers were very well supplied with ascorbic acid, as might have been expected from the large amounts of vegetables and vegetable soups eaten by most families.

It is just possible that the small volumes of milk secreted may have been one reason for the high values for ascorbic acid in this series, since Ingalls, Draper and Teel (1938) found that the milk of mothers producing large amounts of milk tended to contain lower concentrations of ascorbic acid than the milk of those producing small amounts. The evidence for this relationship, however, is not sufficiently definite to invalidate the main conclusion.

Vitamin A. The mean value for this vitamin was almost 40 I.U. per g. of fat in Wuppertal, and about 32 I.U. per g. of fat in England. This difference may have been due to more than one factor. Firstly, it was shown by Kon and Mawson that the amount of vitamin A per g. of fat tended to be high in samples of milk which contained a low percentage of fat, and the percentage of fat in the milk samples taken in Wuppertal tended to be lower than that in samples taken in either Reading or Shoreditch. Secondly, most of the German women were taking large amounts of vegetables, and these may have provided them with so much carotene that they had greater reserves of vitamin A than the English women.

THE COMPOSITION OF BREAST MILK

Women in Early Lactation

Estimations of nitrogen, fat and calcium were made in milk secreted by women in the Landesfrauenklinik, Wuppertal, on the eighth day of lactation. The women were receiving the institutional diet and were the subjects of an investigation on the possible effect of supplements of margarine or of sugar and bread on the secretion of fat in milk (see p. 391). The protein and calcium contents of the milk secreted were unaffected by the supplements, and the mean values for the samples from all women are therefore available for comparison with other standards. Figures for the fat were taken only from the ten women in the control group.

Results

Protein. The mean amount of protein (1·65 g. per 100 c.c., S.E. 0·033) in the milk of the 32 German women in this investigation comes within the range of the values which have been reported in the literature. The figures given below for comparison have been adjusted where necessary to a nitrogen conversion factor of 6·25, the factor used in this investigation. Schlossmann (1900) found the protein content of the milk of 6 women to average 1·81 per cent on the ninth-tenth day; Holt, Courtney and Fales (1915), whose 4 cases were studied between the fifth and twelfth days, reported the higher average figure of 2·19 per cent; Hammett (1917), who sampled the milk on the seventh day, found the average for 8 women to be 1·58 per cent; the protein in the milk examined by Lowenfeld, Widdows, Bond and Taylor (1927) ranged from 1·7 to 2·1 per cent in 3 mothers on the eighth day and Bell (1928) found an average of 1·70 per cent in her extensive series of 88 cases on the ninth day. Macy's (1949) average was 1·56 per cent for milk secreted between the fifth and tenth days.

Fat. Unfortunately few others have analysed milk on the eighth day of lactation, and since 24-hour samples are necessary if the percentage of fat is to be investigated, there are very few figures with which the present results can

be compared. It is believed that the unequal intervals between the times of withdrawing the milk in the present investigation do not invalidate comparisons, provided again that figures relating to secretion during 24 hours are used. The average amount of fat in the milk of the control group of the present investigation was 2·87 g. per 100 c.c. (S.E. 0·189). Söldner and Camerer (1896) gave figures showing an average of 2·97 per cent for 3 women on the eighth and ninth days *post partum*; Holt *et al.* (1915) reported the average percentage of fat in the milk of 4 women between the fifth and twelfth days to be 3·05.

Calcium. The average concentration of calcium in the milk also came within the range of reported values, and again was among the lowest. After adjusting the figures where necessary to make results for calcium oxide comparable with those for calcium, the following figures are obtained: 27·2 mg. calcium per 100 c.c. milk (S.D. 5·1) (present investigation, 32 women); 31·4 mg. for 12 women between the tenth and thirtieth days (Hunaeus, 1909); 27·1 mg. for 8 women, time unstated (Schloss, 1911); 31·8 mg. for 5 women between the first and twelfth days (Holt *et al.*, 1915); 32·8 mg. for 3 women on the seventh day (Lowenfeld *et al.*, 1927); 32·2 mg. for 7 women between the third and eighth days (Rothwell, 1927); 29·3 mg. for 53 women between the eighth and tenth days (Widdows, Lowenfeld, Bond, Shiskin and Taylor, 1935); and 27·6 mg. (S.D. 5·9) for 13 women in the second week and 29·9 mg. (S.D. 4·2) for 76 women between the fifth and twenty-eighth weeks (Kon and Mawson, 1950). Macy (1949) found an average of 46·4 mg. per 100 c.c. for milk secreted between the fifth and tenth days, a value which is considerably higher than those given above.

THE EFFECT OF SUPPLEMENTING THE DIET ON THE YIELD AND COMPOSITION OF MILK

Subjects and Sampling

Women delivered in the Landesfrauenklinik, Wuppertal, were the subjects for these experiments. They were selected for their willingness to co-operate and if it was thought that their breasts would be easy to milk on the eighth day. The institutional diet at the time was composed approximately of 76 g. of protein, 34 g. of fat and 420 g. of carbohydrate, giving a total of 2,235 Calories a day. Eleven women (Group A) were given a supplement of 150 g. of vitaminized margarine daily from the day after delivery until the conclusion of the experiment. Eleven women (Group B) had a supplement of the same Calorie value (1,190 Calories) but consisting of sugar and white bread, usually 200 g. and 150 g. respectively; the bread yielded 13 g. of protein or less. The ten women in Group C acted as controls and received no dietary supplement, but were rewarded for their co-operation by gifts of baby clothes. It was impossible to insist on random selection by putting every third woman into a particular group, for the choice depended mostly on the position of empty beds, and it was considered advisable to give only one kind of supplement in any one room. Nevertheless, there was no selection by performance and as far as possible the age and parity of the mothers in the groups were matched up. The control group of mothers were chosen on about the sixth day. The average age in Group A was 30·2 years (S.E. 2·2); in Group B it was 24·2 years (S.E. 1·45); and in Group C 28·3 years (S.E. 2·02). There were five primagravidae in Groups A and C, and seven in Group B. The food supplements were eaten for the most part between 10 a.m. and 1 p.m.; any food left over was eaten at tea-time. Some difficulty was experienced in finding older mothers who would undertake to

eat the sugar. One woman was unable to eat her carbohydrate supplement and withdrew from the investigation after 24 hours; there were originally eleven women in the control group but one was ultimately rejected because the volume of milk obtained by expression on the day of sampling was only a quarter of that taken by the baby from the other breast on that day, or from that breast on the previous day.

The milk from one breast was removed by manual expression throughout one complete day, as a rule on the baby's eighth. The breast which the baby had taken at the 9 a.m. feed was emptied by hand by approximately 10 a.m., and again by 3 p.m., 5 p.m., 9 p.m., and 10 a.m. the next morning. The baby fed from the other breast at the customary times, i.e. at 5 a.m., 9 a.m., 1 p.m., 5 p.m. and 8.30 p.m. All the mothers were under the care of the same nurses and received the same management. The babies' weights were recorded daily, and in addition they were weighed before and after every meal. The babies of the mothers in Group A averaged 3,398 g. at birth and 3,198 g. on the eighth day; those of the mothers in Group B, 3,206 g. at birth and 3,082 g. on the eighth day, and the corresponding weights for the babies in the control series were 3,430 g. and 3,190 g.

Results

Table 6 gives the average volume of milk obtained, expressed both as c.c. per 24 hours and as a percentage of the milk taken from the other breast by the baby. The mean amounts of fat, protein and calcium in 100 c.c. milk are also shown. The average volume secreted by Group A was smaller than the volumes secreted by the other groups and the babies of that group were on average further below their birth weight on the eighth day than were the babies of the

TABLE 6

The effect of supplementing the diets of women after delivery on the volume and composition of the milk secreted on the eighth day

Group	Food supplement	Average volume of expressed milk (c.c./day)	Average volume of expressed milk as percentage of milk taken from other breast	Fat (g./100 c.c.)	Protein (g./100 c.c.)	Calcium (g./100 c.c.)
A	Fat	175·8 (S.D. 47·0)	92·0	3·15 (S.D. 0·58)	1·63 (S.D. 0·24)	26·2 (S.D. 4·9)
B	Carbohydrate and protein	226·2 (S.D. 79·0)	95·0	3·25 (S.D. 0·70)	1·71 (S.D. 0·15)	27·4 (S.D. 4·8)
C	None	257·8 (S.D. 81·0)	101·5	2·87 (S.D. 0·60)	1·65 (S.D. 0·18)	28·1 (S.D. 4·7)

other two groups. The slightly greater volume of milk secreted by the women in Group C may have been due to the fact that the Group was composed of women who were chosen a few days after delivery and therefore were more likely to be lactating successfully.

The average amount of fat in the milk secreted in 24 hours by the women in Group A was 3·15 g. per 100 c.c. and in Group B 3·25; both values were slightly

TABLE 7

The effect of supplementing the diet with fat (Group A) or with carbohydrate and protein (Group B) on the composition of the milk at different times of day

Time	Group A			Group B			Group C (Control)		
	Average volume (c.c.)	Fat (g./100 c.c.)	Protein (g./100 c.c.)	Average volume (c.c.)	Fat (g./100 c.c.)	Protein (g./100 c.c.)	Average volume (c.c.)	Fat (g./100 c.c.)	Protein (g./100 c.c.)
10 a.m.–3 p.m.	39·4	3·55	1·71	46·2	3·63	1·74	48·4	3·22	1·79
3 p.m.–5 p.m.	19·7	3·76	1·67	27·6	3·82	1·78	23·9	3·43	1·73
5 p.m.–9 p.m.	28·6	3·25	1·59	42·6	2·99	1·69	38·9	2·55	1·63
9 p.m.–10 a.m.	85·0	2·76	1·62	109·8	3·02	1·67	123·2	2·62	1·58

higher than the average of 2·87 g. per 100 c.c. found in the milk of the control group, but the differences based on the small number of observations were not significant. Table 7 shows that the percentage of fat in the milk from the supplemented groups averaged a little more than that from the control group, not only over 24 hours, but at each milking time. The consistency with which the percentage of fat in the milk from the supplemented groups exceeded that from the control group suggests that the food supplements had had some effect, but the differences were not significant, except for the difference between the averages for the samples taken at 9 p.m. from the control group and the group receiving fat. This was greater than that conventionally attributed to chance. No correlation was found between the percentage of fat in the milk and the parity of the mothers or the volume of milk secreted. It is to be noted that, owing to the smaller volume of milk produced by the women receiving the fat supplement, the total amount of fat secreted per day was considerably lower in this group than in either of the other two.

Total nitrogen was estimated in the four samples of milk from 27 of the 32 women and in three samples from 3 others. No significant difference was found between the three groups of mothers. A regression coefficient of the variation of the mean percentages of protein and fat in 24 hours showed a significant correlation. In woman's milk, then, as in cow's milk, richness in fat is on the whole associated with a high percentage of protein, although the relation is not sufficiently consistent to enable one figure to be deduced from the other. In contrast to the fat content, the protein content varied very little between one time of day and another.

It was noticed that in some individuals the amount of protein was quite variable and in others almost constant. Since the serum protein varies so much with posture and since some patients were up for much of the day and others still almost completely confined to bed it seemed possible that the variations might be related to posture. The one experiment made to investigate this possibility did not confirm it.

Relation of the birth weight, the volume of milk taken and the percentage of fat in the milk to gain in weight. A statistical analysis was made to investigate the influence, if any, of three factors upon the baby's return to birth weight. Multiple partial regression coefficients were calculated to show the relation of the total volume of milk taken by the baby, the percentage of fat in the milk and the baby's birth weight to the amount by which the baby was below its birth weight on the eighth day (see Appendix to this section). The regression coefficients show that the birth weight was the main factor, a large baby taking longer to regain that weight. Volume of milk taken was also important, but the percentage of fat in the milk on the eighth day was not related significantly to the regain of weight. It may be objected that since the amount of fat in milk changes rapidly in the first days after birth the amount found on the eighth day is not a representative figure for the first week. It seems fair to conclude, however, that in the days when success or failure of lactation is largely being determined, the rate at which the baby regains its birth weight depends mainly on the volume of milk and that the percentage of fat, in spite of wide variations, has little effect.

DISCUSSION

The early part of this work indicated that single samples of milk taken from Wuppertal women in established lactation showed no significant differences in

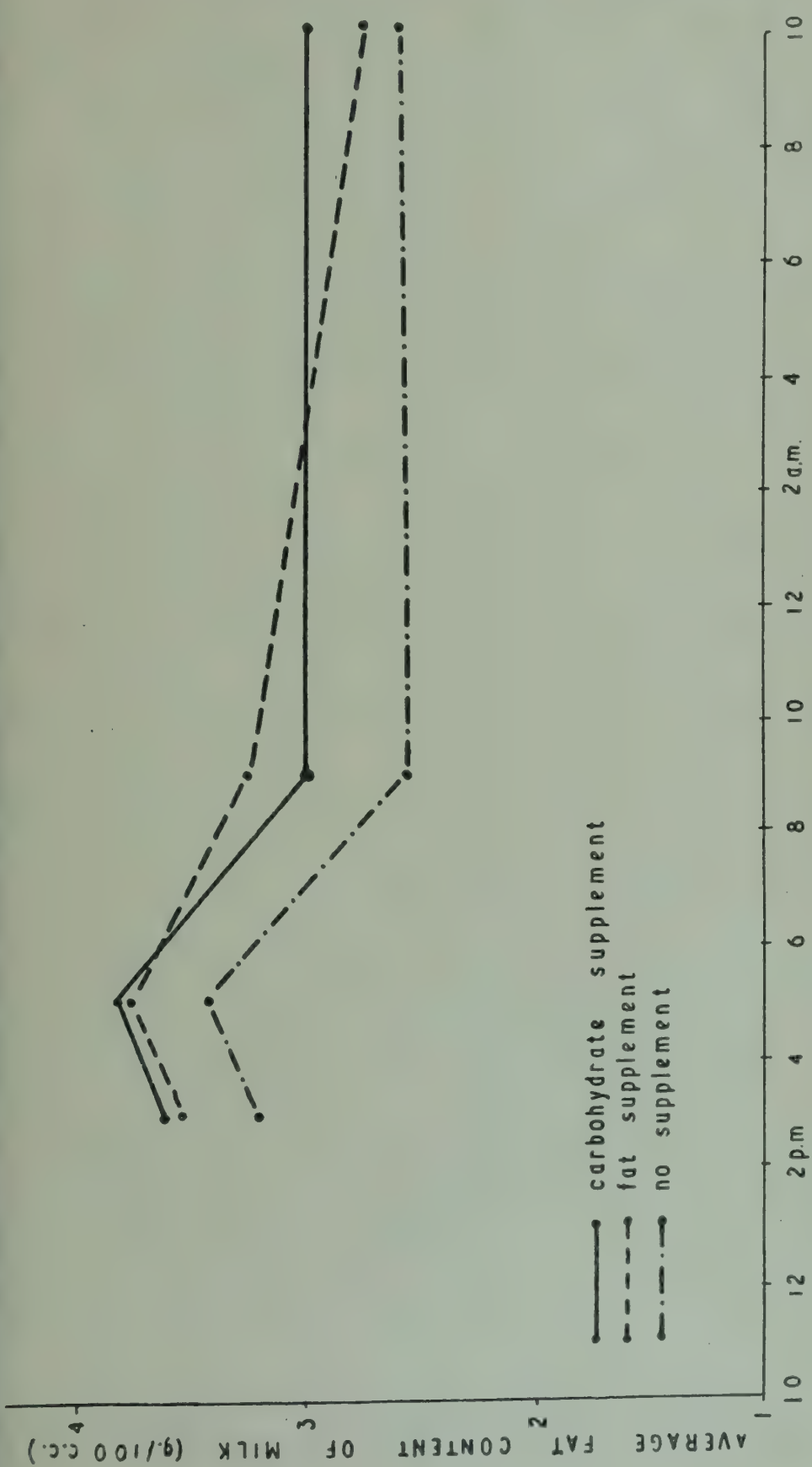

FIG. 1. Diurnal variations in the average amount of fat in the milk of women receiving dietary supplements (8th day after delivery).

composition from similar samples taken from English women. The milk from women in early lactation also seemed to be normal in composition as regards protein, fat and calcium. It was realized, however, that factors such as time of day and the completeness with which the breast is emptied affect the composition of the milk to such an extent that satisfactory comparisons can only be made of 24-hour samples. It was also clear that any study of the effect of dietary supplements on the composition of the milk must be made on 24-hour samples, which could only conveniently be obtained from women in hospital in early lactation.

The food supplements given in the investigation increased the Calorie intake from about 2,200 to 3,300; the fat supplement increased the fat intake fivefold and was as much as the mothers could comfortably eat. The supplements, therefore, were large enough to affect the composition of the milk if an immediate insufficiency of dietary fat, carbohydrates or Calories was impoverishing it. It must be concluded therefore that for women on daily diets of 420 g. of carbohydrate, 76 g. of protein and 34 g. of fat, further Calories in the form of sugar and white bread or of vitaminized margarine, given from the time of delivery, did not appreciably affect the quality of milk secreted over the whole day in early lactation.

In the sample taken at 9 p.m., however, the average percentage of fat in the milk from the group receiving fat was higher than that from either of the other groups at that time (see Fig. 1). The milk of this sample was presumably formed between 5 p.m. and 9 p.m. and the fat supplement had been eaten mostly between 10 a.m. and 1 p.m. The time between the taking of the fat and the formation of the milk which had a relatively high percentage of fat in it (6–12 hours) is roughly the same as that reported by Ruzicic (1936), who found that dietary fat had a very striking effect on the composition of breast milk. Since in dogs the fat in the bloodstream is said to reach a maximum some 6 hours after ingestion of fat (Wright, 1937), and since in cows neutral fat has been thought to be taken up from the circulating blood by the active mammary gland (Graham, Jones and Kay, 1936), there are grounds for thinking that the fat supplement did raise the percentage of fat in the milk secreted in the evening. The effect, however, was so small and diurnal variations so far exceeded any change which might have been attributed to the eating of fat, that the intake of fat does not seem ordinarily to determine the percentage of fat found in milk. In support of this statement it may be added that the average amount of fat secreted by the 21 women in the control and carbohydrate groups was 14·2 g. per day compared with an intake of 34 g. The greatest amounts secreted by individual women were 27·8 g. and 26·7 g., if it is assumed that the secretion from the two breasts was the same. One woman on the same diet who was not a subject of this investigation but whose milk was analysed on the eighth day when secretion was abundant, was secreting approximately 36 g. of fat on an intake of 34 g. The fat of breast milk is therefore thought to be synthesized in part at least from carbohydrate or carbohydrate derivatives or to be obtained by mobilization of fat from other parts of the body. In this connexion the reports that the mammary gland of the ruminant uses acetate for milk-fat synthesis are interesting (Folley and French, 1950).

The effect which the ingestion of fat had on the composition of the milk in Ruzicic's cases may have been a secondary result of the very large size of the dose. In one investigation (Ruzicic, 1934), two women had a definite increase in the percentage of fat in their milk, and with it a great reduction in the volume of

milk secreted, on the days when they took nothing but 450 g. (about 1 lb.) of butter. In one woman the daily volume of milk secreted fell from 3,100 to 1,820 c.c. when she took 450 g. of butter and 750 g. of meat per day, and the percentage of fat in the milk secreted in 24 hours rose from 3·0 to 5·7. Similar effects on both the composition and the volume of the milk were also produced in the same women by two days' starvation. Various workers have reported similar changes in the composition and volume of milk secreted by cows suffering from ketosis. In view of the enormous doses of fat taken by Ruzicic's subjects there seems to be good reason to believe that the changes observed by him were due to ketosis rather than to mere availability of fat. The same explanation may be offered for the high percentage of fat reported by Schukowski (1871) in the milk of fasting women. In the present investigation acetone was not detected in the breath of the German mothers who received extra fat, and since they were also receiving about 400 g. of carbohydrate daily it is thought that they were free from ketosis.

SUMMARY

The Composition of the Milk

1. The amounts of ascorbic acid, riboflavin and total nitrogen in the milk of about 60 German women in full lactation in the autumn and winter of 1946–7 were similar to those reported by Kon and Mawson in the milk of English women between 1941 and 1945. Mean values for ascorbic acid varied between 3·2 and 4·3 mg. per 100 c.c. at different times of the year, for riboflavin between 18·8 and 25·1 μg. per 100 c.c. according to conditions of sampling, and for total nitrogen between 227 and 186 mg. per 100 c.c. according to the stage of lactation.

2. The mean value for total aneurin was 19·4 μg. per 100 c.c. as against the English value of 18·3, and for vitamin A about 40 I.U. per g. of fat as against the English value of about 32. Possible explanations for these relatively high values are considered.

3. The percentage of fat was lower in milk obtained from women in full lactation in Germany than in that obtained in England, but this may have been due to the differences in sampling technique and cannot at present be attributed to undernutrition.

4. The percentage of fat in milk on the eighth day of lactation was close to the values found by the other investigators. The percentage of protein was within the range of the values which have been reported for that stage of lactation. The calcium did not differ significantly from other reported values.

The Effect of Supplements

1. Supplements of 150 g. of fat or the Calorie equivalent in the form of bread and sugar daily during the puerperium did not significantly alter the percentage of fat or protein in the milk secreted on the eighth day.

2. The rate at which babies regained their birth weights depended upon the volume of milk they drank and not upon the percentage of fat in it on the eighth day.

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APPENDIX

Statistical Details of the Inter-relation between the Baby's Return to Birth Weight, the Birth Weight, the Fat Content of the Milk on the Eighth Day and the Total Volume of Colostrum and Milk Taken by the Baby up to the Eighth Day

The regression of the amount by which the baby was under its birth weight on the eighth day was worked out on the three variates (1) birth weight, (2) fat content (g. per 100 c.c.) of the milk and (3) total volume of milk. There were no significant differences between the three diet groups. Accordingly, using the regression calculated from the data as a whole, the following figures were found:

	Coefficient	*Standard error*
b_1	−0·1083	0·031
b_2	1·4310	25·65
b_3	0·1485	0·037

This gives a regression

$Y = 143{\cdot}4 - 0{\cdot}108\ (x_1 - 1642) + 1{\cdot}431\ (x_2 - 3{\cdot}098) + 0{\cdot}148\ (x_3 - 3342)$

with a standard deviation of prediction of 89·7. The standard deviation of Y is 116·9 and the comparison of the two gives a concrete idea of the value of the regression equation. The multiple correlation coefficient is 0·685. The regression coefficient b_2 on fat content is quite insignificant and is better omitted. This modifies the other values of b slightly and we find $b_1 = -0{\cdot}1084$

$b_3 = +0{\cdot}1481$

Accordingly, the regression equation is now

$Y = 143{\cdot}4 - 0{\cdot}108\ (x_1 - 1642) + 0{\cdot}148\ (x_3 - 3342)$.

The S.D. of prediction is now 88·1, very slightly smaller, and the multiple correlation coefficient 0·684.

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APPENDIX

LABORATORY TECHNIQUES

SPECIALIZED laboratory techniques used for one investigation only are described in their own sections, but others, which were in general use throughout the time the Unit was in Wuppertal, and which were employed in a number of different investigations, are described below. Duplicate samples of all materials were taken for all chemical determinations.

Collection of Blood

Venous blood taken from the antecubital vein of the arm with a 19 B.W.G. needle attached to a piece of rubber tubing was used for all determinations. The blood was allowed to run out freely, with the minimum of constriction. A syringe was never used. Clotting was prevented with 0·02 g. of a mixture of 2 parts of potassium oxalate and 3 parts of ammonium oxalate per 10 c.c. of blood.

When serum was required the whole blood, without the addition of any anti-coagulant, was centrifuged within an hour of collection. Blood for the determination of serum chlorides was collected under liquid paraffin without any constriction.

Preservation of Urine

Urine was preserved under toluene.

Food and Faeces for Metabolism Experiments

Duplicate samples of all foods and the week's collection of faeces were preserved and dealt with as described by McCance and Widdowson (1942).

Haemoglobin

The method of Gibson and Harrison (1945) was used. Determinations were always made in duplicate on the day on which the blood was collected, but the two samples were always placed in different groups of estimations and matched against different standards.

Haematocrit

Triplicate samples of blood were centrifuged in pieces of capillary tubing sealed at one end with Plasticine at 3,000 r.p.m., at a mean distance of 10 cm. from the axis of rotation, for 45 minutes, and the lengths of the columns of cells and plasma were measured on millimetre graph paper. The estimations were always made on the day on which the blood was collected.

Urea

The urea in blood filtrates and in urines was determinated by Lee and Widdowson's (1937) or by Archibald's (1945) method. For the former, the proteins in the whole blood or serum were precipitated with tungstic acid; for the latter, cadmium sulphate was used. The two methods gave satisfactory agreement when used for the analyses of identical samples.

Nitrogen

Nitrogen was estimated by the standard micro-Kjeldahl technique, using copper selenide as catalyst. To facilitate proper sampling in the metabolism experiments, a portion of the mixed foodstuffs was boiled with 2 per cent H_2SO_4 under a reflux condenser for several hours, the mixture was made up

to a known volume and an aliquot was taken for the nitrogen determination. The mixed faeces (20 g.) were weighed out into small beakers, stirred up with 10 c.c. conc. H_2SO_4 and left to stand for several days. The mixture was then made up to 500 c.c. in a volumetric flask and the nitrogen estimation was made on an aliquot.

Serum Proteins

Total protein. A measured volume (0·5 c.c.) of serum was diluted with 7·5 c.c. of normal saline, and the protein was precipitated with 1 c.c. of a 10 per cent solution of sodium tungstate and 1 c.c. of 2/3N-H_2SO_4. The precipitated protein was separated by centrifugation, and dissolved in 1–2 c.c. N/10 NaOH. This solution was washed into a 50 c.c. graduated flask and made up to volume. Nitrogen was determined in 5 c.c. of the solution.

TABLE 1

A comparison of the concentration of albumen found in sera when magnesium and sodium sulphates were used for the fractionation

Serum No.	Albumen (g./100 c.c.)	
	Magnesium sulphate	Sodium sulphate
1	5·63	5·62
2	4·47	4·65
3	4·78	4·91
4	5·09	5·00
5	5·31	5·31
6	4·50	4·52
7	4·39	4·58
8	5·62	5·65
9	5·43	5·45
10	4·85	4·67
11	4·66	4·75
12	4·53	4·53
Average	4·94	4·97

Albumen and globulin fractionation. Serum (1 c.c.) was mixed with 14 c.c. of a saturated solution of magnesium sulphate containing some crystals of the salt, and left to stand overnight. The precipitated globulin was filtered off through a Whatman No. 542 filter paper, and the albumen from 5 c.c. of the clear filtrate was precipitated with 1 c.c. of a 10 per cent solution of sodium tungstate and 1 c.c. of 2/3N-H_2SO_4. The precipitate was centrifuged off, washed with 5 c.c. of distilled water to remove most of the magnesium sulphate, and again separated by centrifugation. It was dissolved in 1 c.c. of N 10 NaOH, washed into a 25 c.c. graduated flask and made up to volume. Subsequent treatment was the same as that described for total protein. The concentration of globulin was calculated by difference.

The albumen and globulin in 12 sera were separated by means of sodium sulphate solution (Howe, 1921) as well as with magnesium sulphate, since sodium sulphate is the reagent more usually employed for the protein fractionation. Table 1 shows the values for albumen which were obtained by the two methods. It will be seen that the agreement is satisfactory.

Chloride

Whitehorn's (1920) method was used for all urines, except where the volumes were too small. For the estimation of the chlorides in serum, or in small samples of urine, the method described by McCance and Shipp (1933) was employed.

Inulin

Inulin in serum and in urine was estimated by a modification of Roe's (1934) method, as described by Bacon and Bell (1948). Protein was removed from the serum with cadmium sulphate.

Diodone

The method of White and Rolf (1940) modified on the lines suggested by Bak, Brun and Raaschou (1943) was used. Cadmium sulphate was chosen for removing the serum proteins, and determinations were carried out directly on the diluted urines without any preliminary treatment.

Freezing Point

Determinations of the freezing point of urine were made with a Beckmann thermometer by the standard technique.

Fat

Fat was determined in foods and dried samples of faeces by the method of von Lieberman and Szekely (1898), as described by McCance and Shipp (1933).

Calcium and Magnesium

Determination of these metals in serum was carried out directly; all other materials such as food, urine, and faeces were first incinerated in silica crucibles overnight at 450° C., and the ash was extracted with HCl as described by McCance and Widdowson (1942). The estimation of calcium was made on the serum or the acid extract of the ash as described by McCance and Shipp (1933). The method described for magnesium by these authors was also used, but instead of dissolving the precipitate of magnesium ammonium phosphate in 1 c.c. of N/10 HCl, a larger volume (2–5 c.c.) of this acid was generally used, and 1 c.c. of the resulting solution was taken for the final determination. In this way the magnesium was precipitated at the correct concentration, but the blue colour at the end was sufficiently pale to be read in a Pulfrich step-photometer.

Total Phosphorus

Phosphorus was estimated by Briggs's (1922) method as described by McCance and Widdowson (1942).

Phytic Acid Phosphorus

Samples of bread and of faeces, dried *in vacuo* at 50° C. and finely ground, were used for the determination of phytic acid phosphorus. The method of estimation was that described by McCance and Widdowson (1935).

Extracellular Fluid Volume

Sodium thiocyanate solution (25 c.c.), containing 1·5 g. of the salt dissolved in distilled water, was injected intravenously, and two hours later a sample of blood was taken and the serum separated. The subjects were encouraged

to move about during the two hours. Urine was collected over this period so that the amount of the thiocyanate which had been excreted could be determined. The estimation of thiocyanate in the serum and the urine was carried out as described by Lavietes, Bourdillon and Klinghoffer (1936) and the extracellular fluid volume was calculated as described by these authors, due allowance being made for the penetration of the thiocyanate into the red blood cells.

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I.G. Farben factory, Wuppertal-Elberfeld.

PLATE II

"Vogelsaue", Wuppertal. The I.G. Farben laboratories are just out of sight at the bottom of the hill.

PLATE III

Ruins of houses in Wuppertal on the south side of the valley. The wooded hills on the north can be seen in the background.

PLATE IV

Cellar dwelling and milk shop.

PLATE V

A small house among the ruins, constructed of salvaged bricks.

PLATE VI

A Bunker, i.e. a large air-raid shelter.

PLATE VII

Political poster in Ronsdorf, 1946.

PLATE VIII

Children waiting at Wuppertal-Oberbarmen station for the returning hamsterers.

PLATE IX

A hamsterer returning home.

PLATE X

An autumn expedition for fruit and potatoes.

PLATE XI

Part of the laboratories of the I.G. Farbenindustrie, Wuppertal-Elberfeld. The Unit worked on the first floor of this block

PLATE XII

Anterior aspect of leg below the knee of a repatriated prisoner of war.

PLATE XIII

Antero-lateral view of calf of a repatriated prisoner of war.

PLATE XIV

Anterior view of lower leg and ankle of a repatriated prisoner of war.

PLATE XV

Lateral view of calf of German civilian, showing large flakes of epidermis ready to separate.

PLATE XVI

Fissured scaly skin from the front of the knee in a repatriated prisoner of war.

PLATE XVII

Follicular changes of the skin of an otherwise normal child.

PLATE XVIII

Folding and elevations together with advanced follicular changes of the skin of a young civilian prisoner.

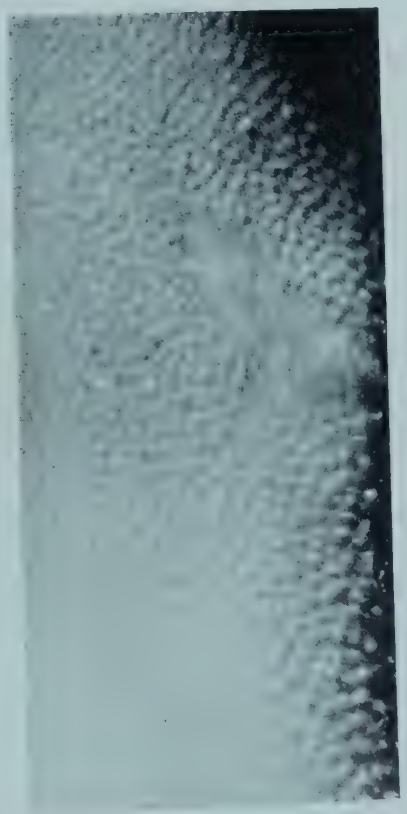
PLATE XIX

Extensive but milder follicular changes of the skin of a civilian prisoner

PLATE XX

Severe hyperkeratosis pilaris and wasting of the buttock of a civilian prisoner.

PLATE XXI



Moderate hyperkeratosis pilaris on the arm of a civilian prisoner.

PLATE XXII

Pigmented, folded and flaking skin over pressure points and in the folds of the buttocks of a repatriated prisoner of war.

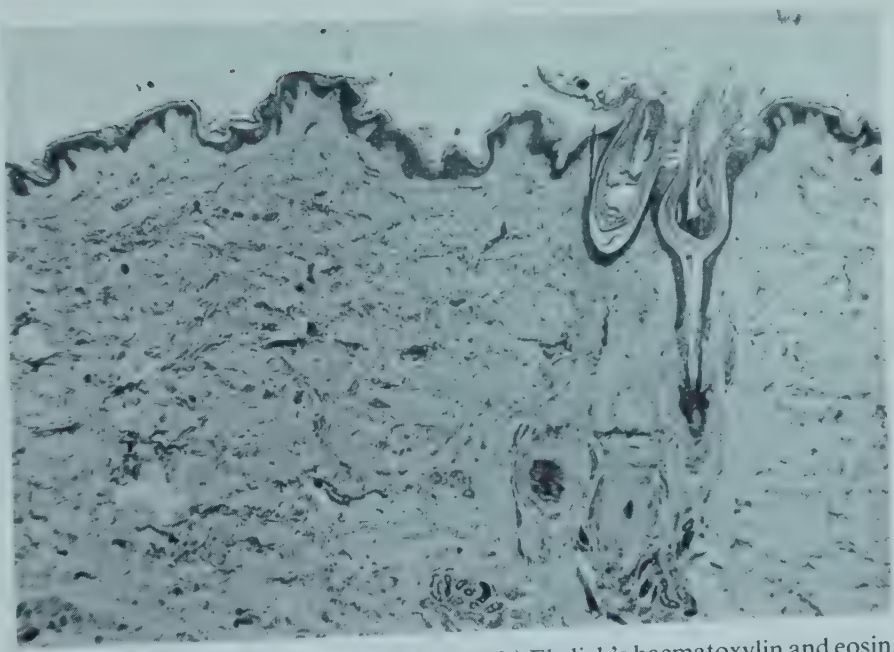
PLATE XXIII

Pigmentation of skin over greater trochanter. Same man as in Plate XXII

PLATE XXIV

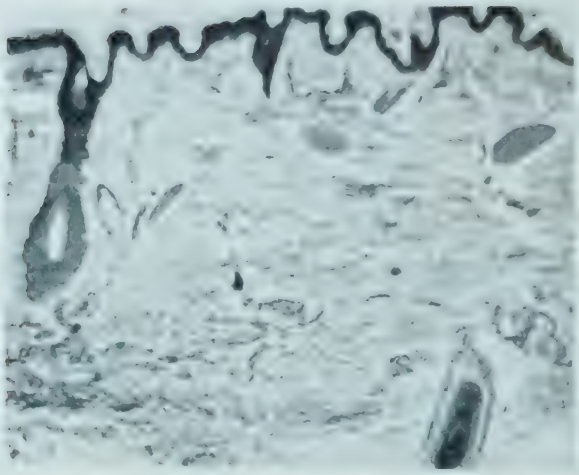
Chronic ulcer in a young man aged 19.

PLATE XXV



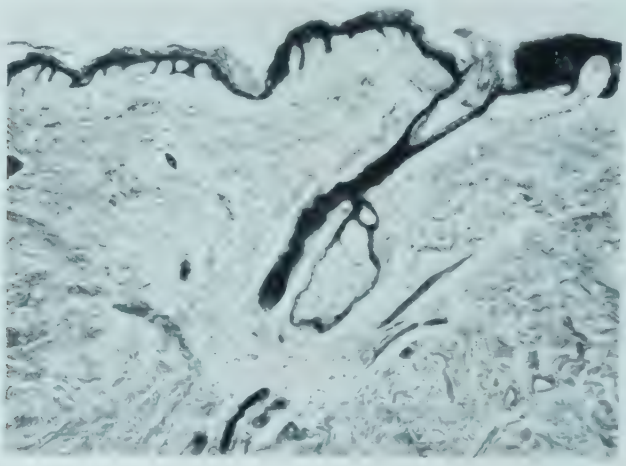
Section of skin shown in Plate XVIII. (× 30.) Ehrlich's haematoxylin and eosin.

PLATE XXVI



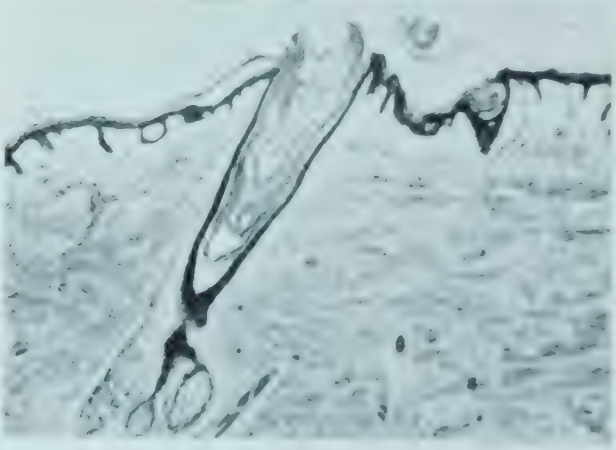
P46 272, English control. Normal skin. (40.) The boundary between the connective tissue of the corium and the subcutaneous adipose tissue is at the bottom of the photograph and the base of the hair follicle at the right is embedded in subcutaneous fat.

PLATE XXVII



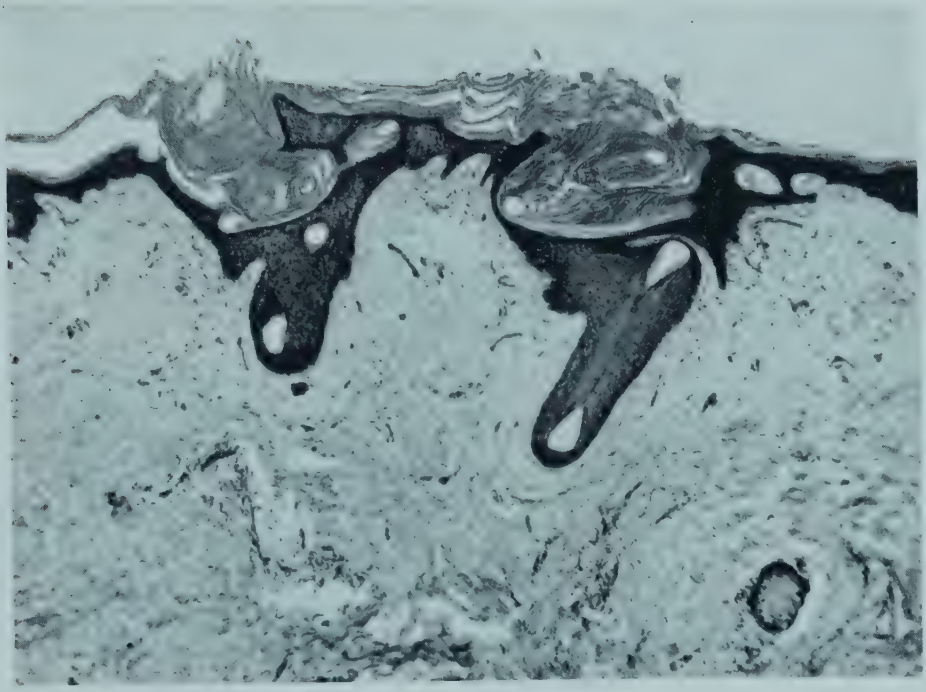
S46 7591, undernourished German. Section of skin showing slight follicular keratosis in the mouth of a small crooked hair follicle, which does not extend nearly to the subcutaneous fat. (× 40.) Ehrlich's haematoxylin and eosin.

PLATE XXVIII



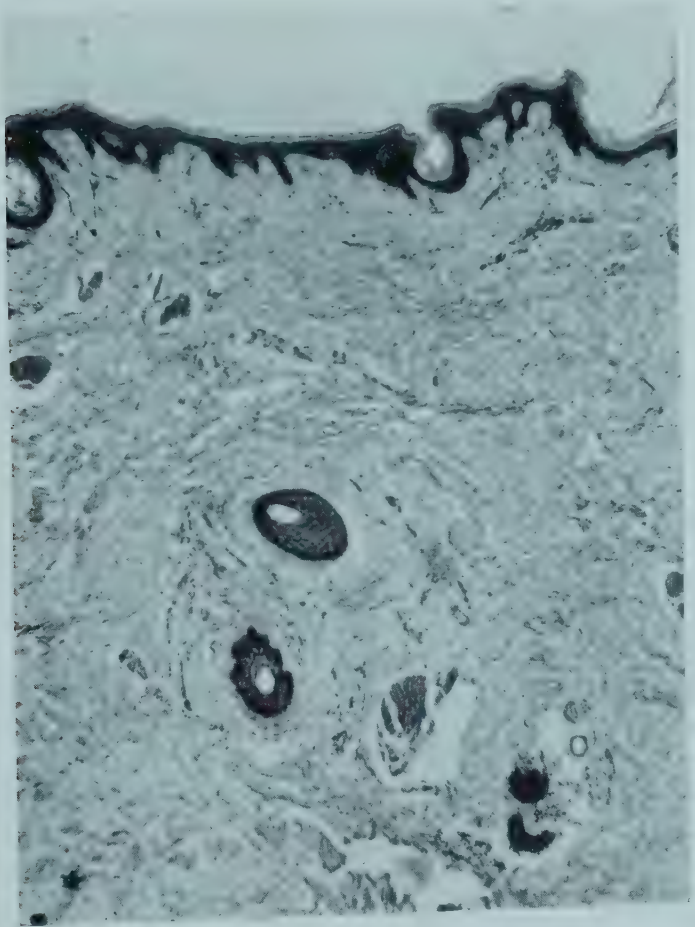
S46/7591, undernourished German. Section showing advanced follicular keratosis with atrophy of hair follicle and sebaceous gland. (× 40.) Ehrlich's haematoxylin and eosin.

PLATE XXIX



S46/7593, undernourished German. Two coiled hairs, each cut four times in this one section, entrapped in keratin at the mouths of the follicles. (× 60.) Ehrlich's haematoxylin and eosin.

PLATE XXX

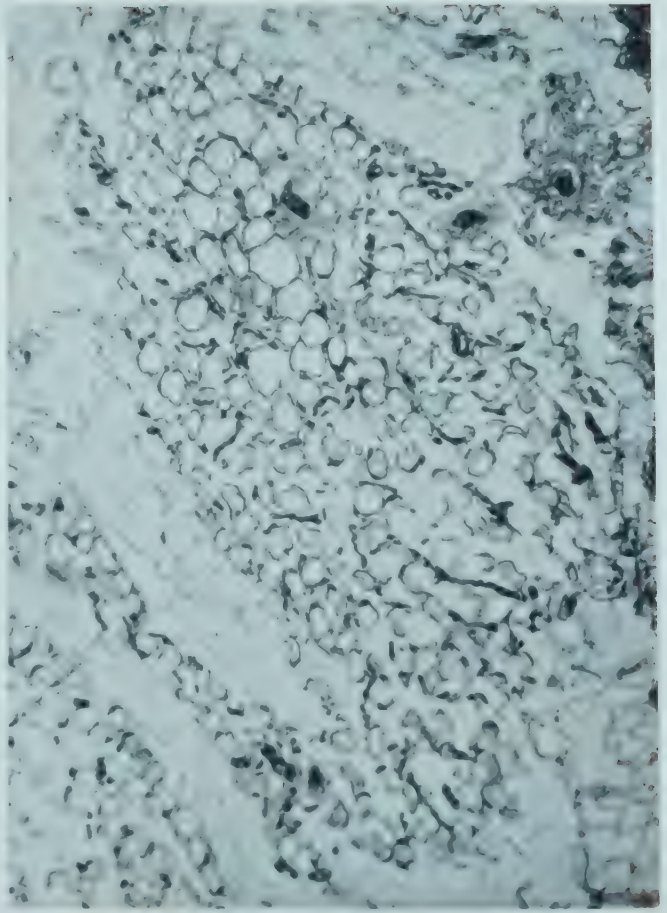


S46/7593, undernourished German. A hair follicle cut twice in a section perpendicular to the skin surface, showing that it was crooked. (× 60.) Ehrlich's haematoxylin and eosin.

PLATE XXXI

P272 46. English control. Section of subcutaneous adipose tissue, for comparison with Plate XXXII. (× 115.) Ehrlich's haematoxylin and eosin.

PLATE XXXII



S46 7591, undernourished German. Section showing subcutaneous adipose tissue depleted of fat. (× 115.) Ehrlich's haematoxylin and eosin.

PLATE XXXIII

B83, undernourished German, prone, 1 hr. after barium meal. Dilatation of the jejunum with wide separation of the rugae. Some clumps of barium and mucus at the head of the column in the lower part of the illustration. The barium column is not quite continuous.

PLATE XXXIV

C1, English control, prone, 54 min. after barium meal. Normal small intestine. Note the fine rugae and the continuous trail in the upper jejunum.

PLATE XXXV

XY, undernourished German, supine, 25 min. after barium meal. The rugae in the upper jejunum are large and widely separated

PLATE XXXVI

B118, undernourished German, supine, 1 hr. 16 min. after barium meal. The rugae are widely separated in the jejunum, where the bowel wall is coated but not filled with barium.

PLATE XXXVII

X19, undernourished German, supine, 1 hr. 55 min. after barium meal. Flocculation in the jejunum and upper ileum. The pattern of the rugae is completely obliterated in the affected areas.

PLATE XXXVIII

B83, undernourished German, prone, 2 hr. 27 min. after barium meal. Large flakes of barium are present in the crevices between the folds in the right upper part of the illustration. This is not flocculation; compare with Plate XXXVII.

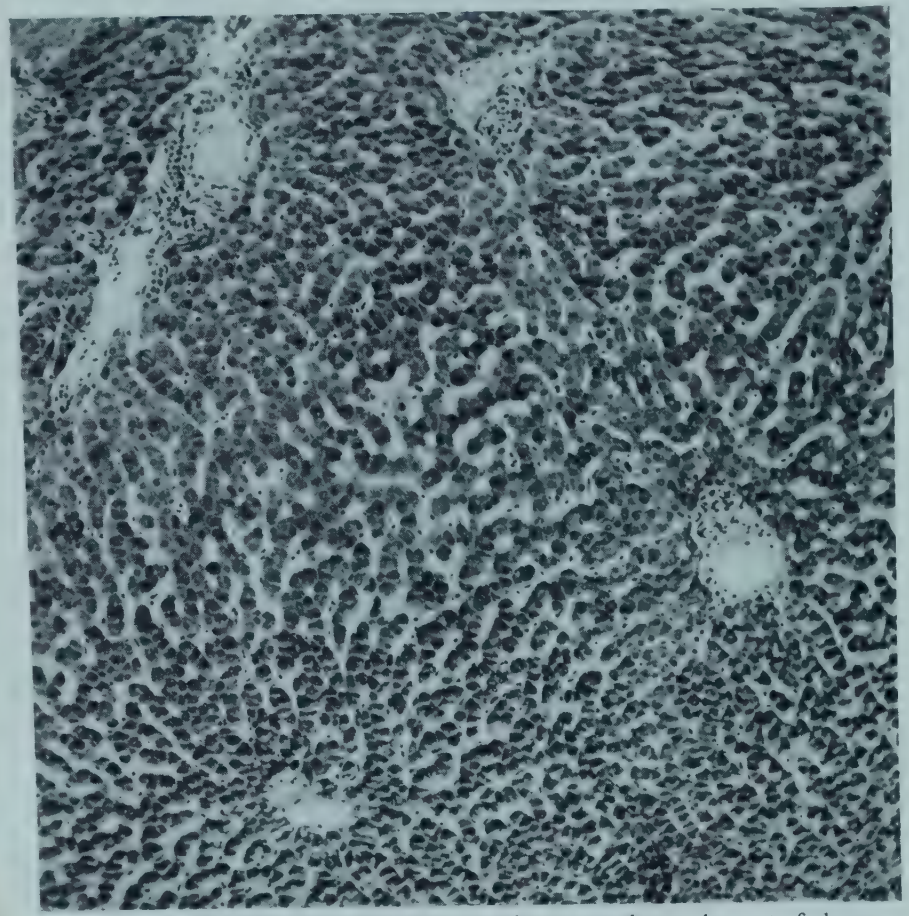
PLATE XXXIX

X28, undernourished German, supine, 2 hr. 15 min. after barium meal. Segmentation in the jejunum. The rugae on the borders of the segments are irregular.

PLATE XL

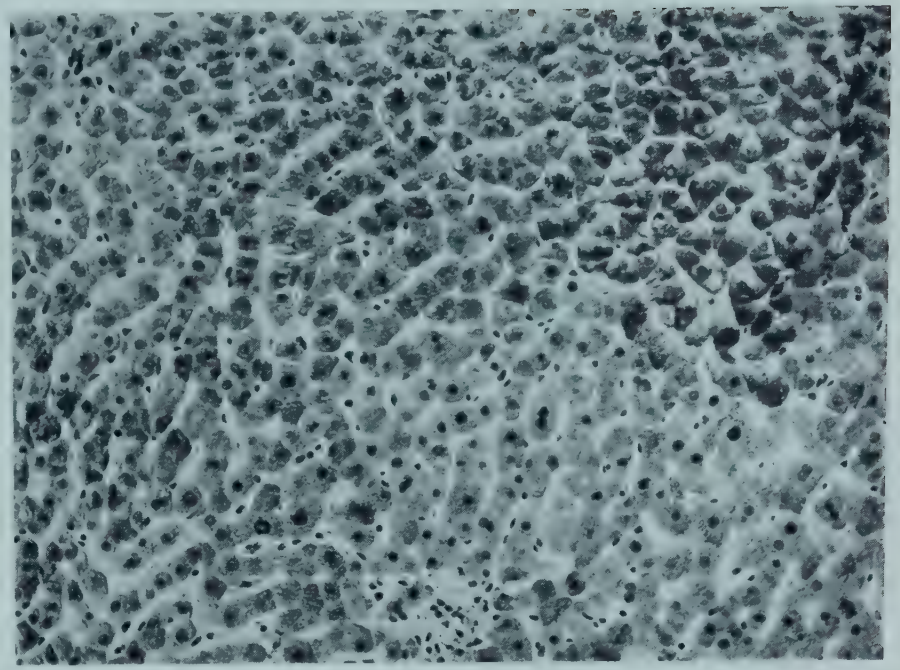
C13, English control, prone, 38 min. after barium meal. Clumps of barium and mucus at head of the barium column in a normal person. The clumps are narrower than the normally outlined loops.

PLATE XLI



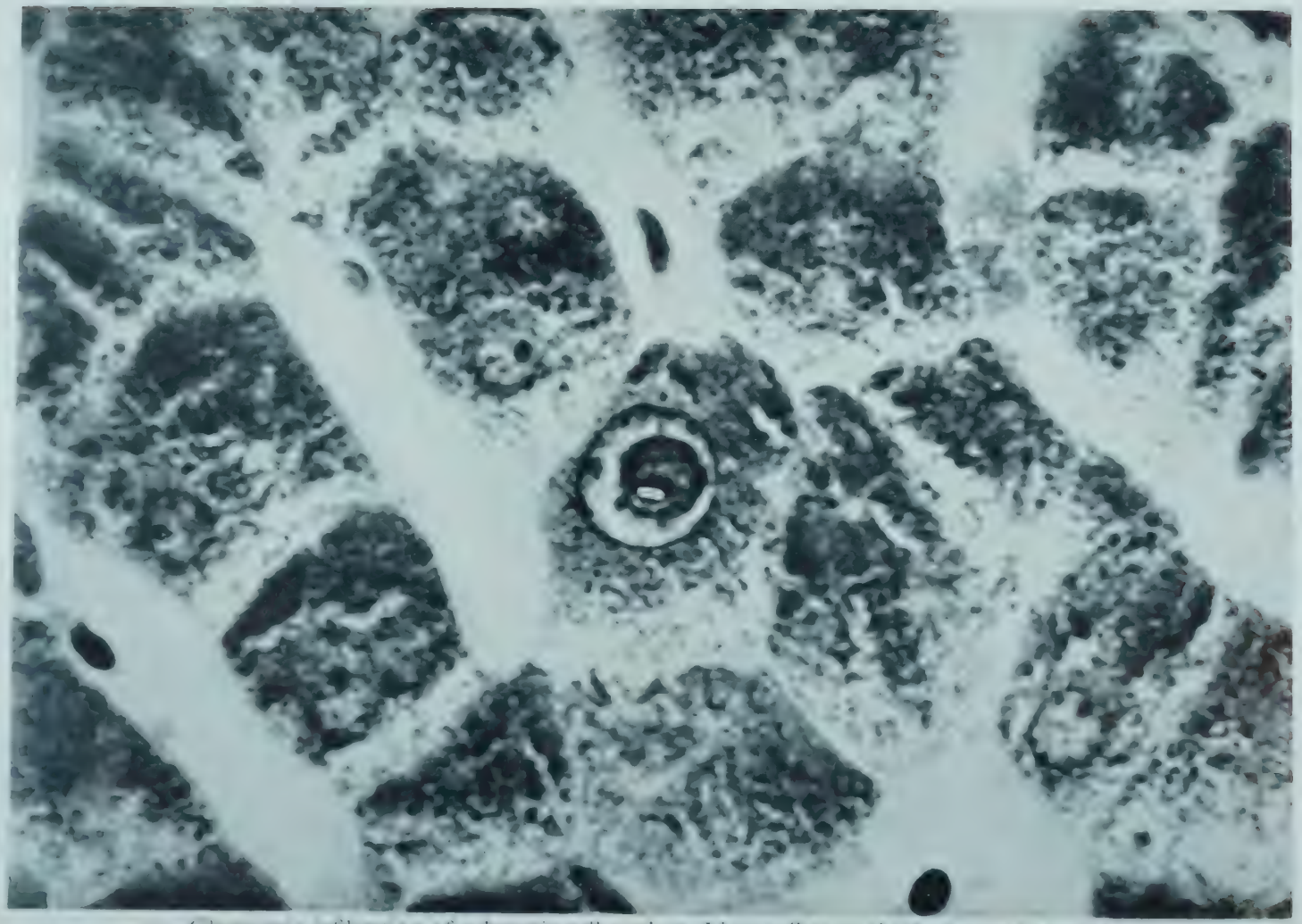
Normal lobular pattern. Hepatic cells contain a normal complement of glycogen. Portal tracts appear normal. Subject 12. Best' s carmine. (× 95.)

PLATE XLII



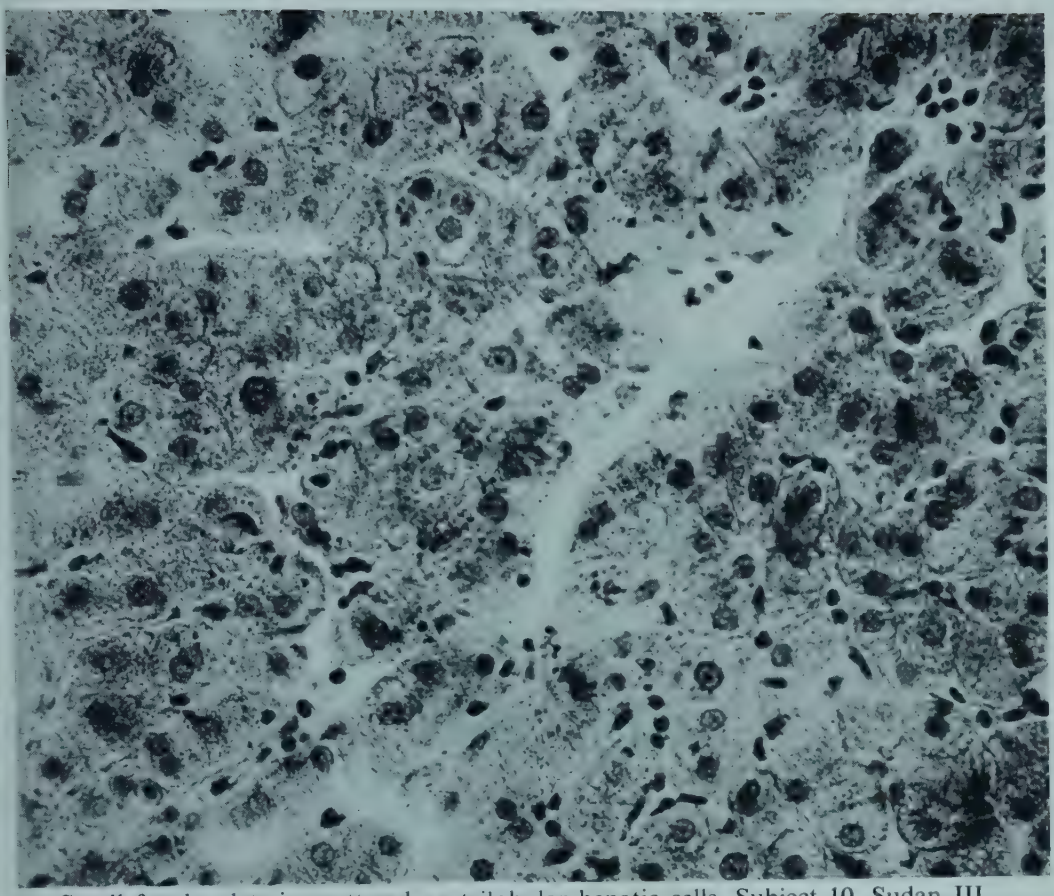
A group of liver cells contain normal amounts of glycogen, others are deficient. Some cells contain pigment granules. Many nuclei are large and hyperchromic. Küppfer cells are prominent. Subject 16. Best's carmine. (× 145.)

PLATE XLIII



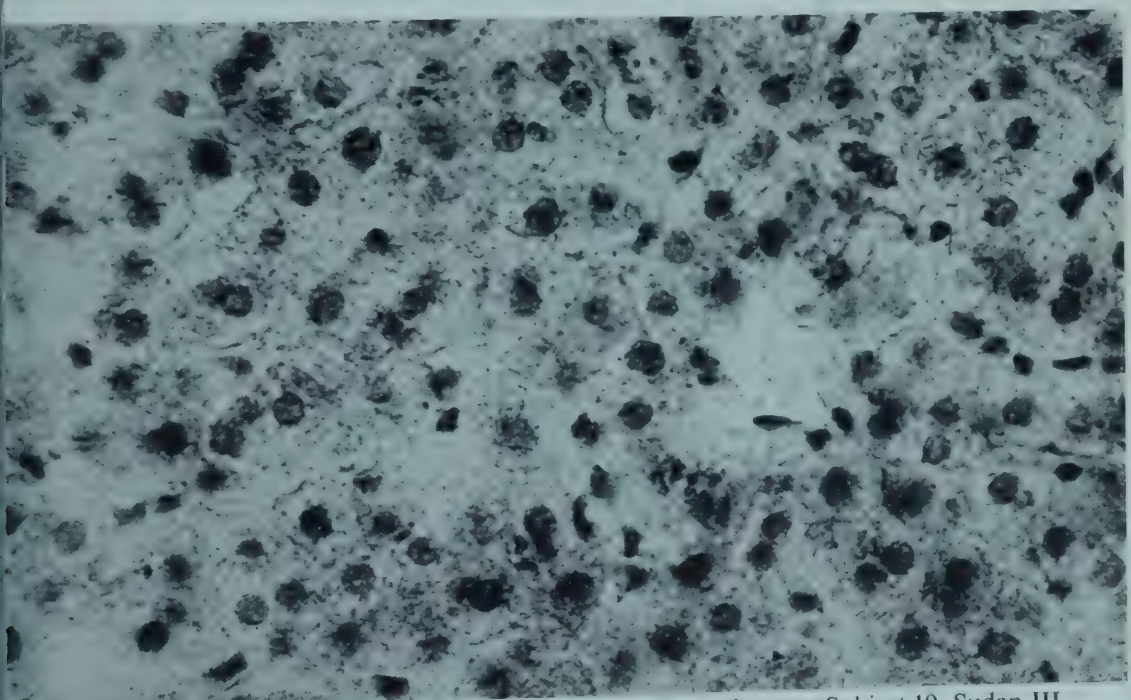
Glycogenic infiltration of a hepatic cell nucleus. Liver cells contain the normal amount of glycogen. Subject 8. Best's carmine. (× 1150.)

PLATE XLIV



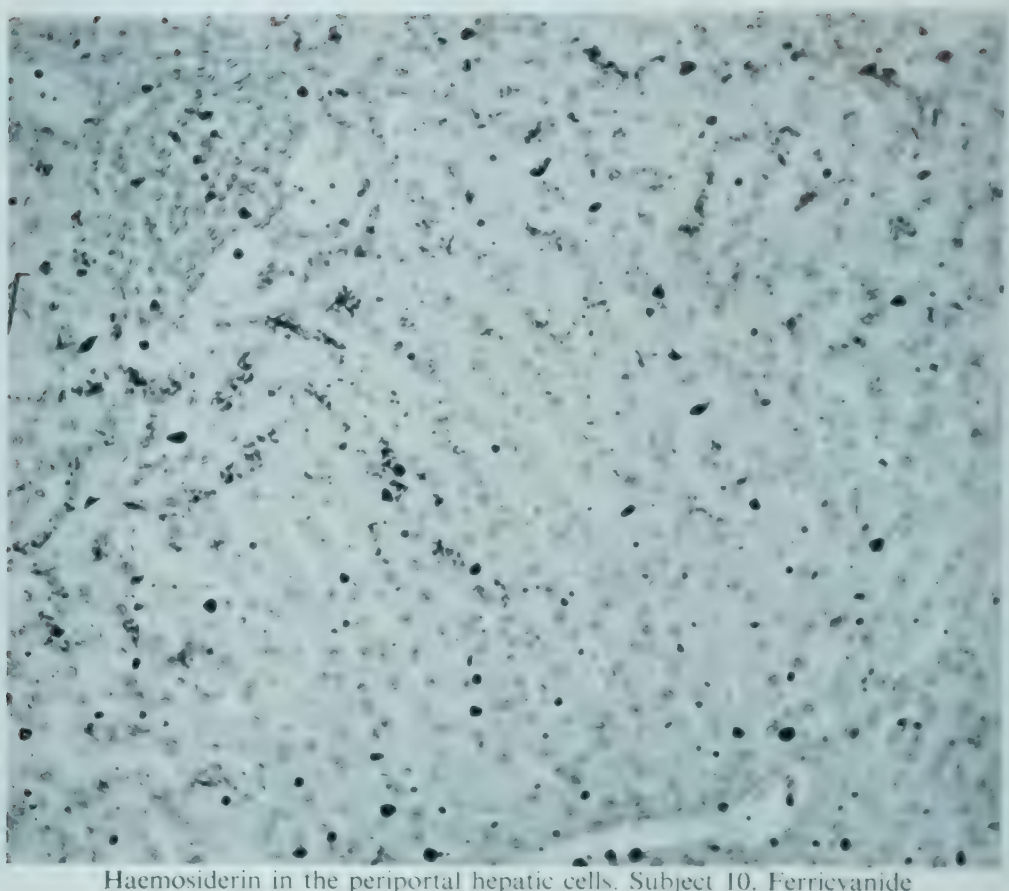
Small fat droplets in scattered centrilobular hepatic cells. Subject 10. Sudan III and haematoxylin. (× 300.)

PLATE XLV



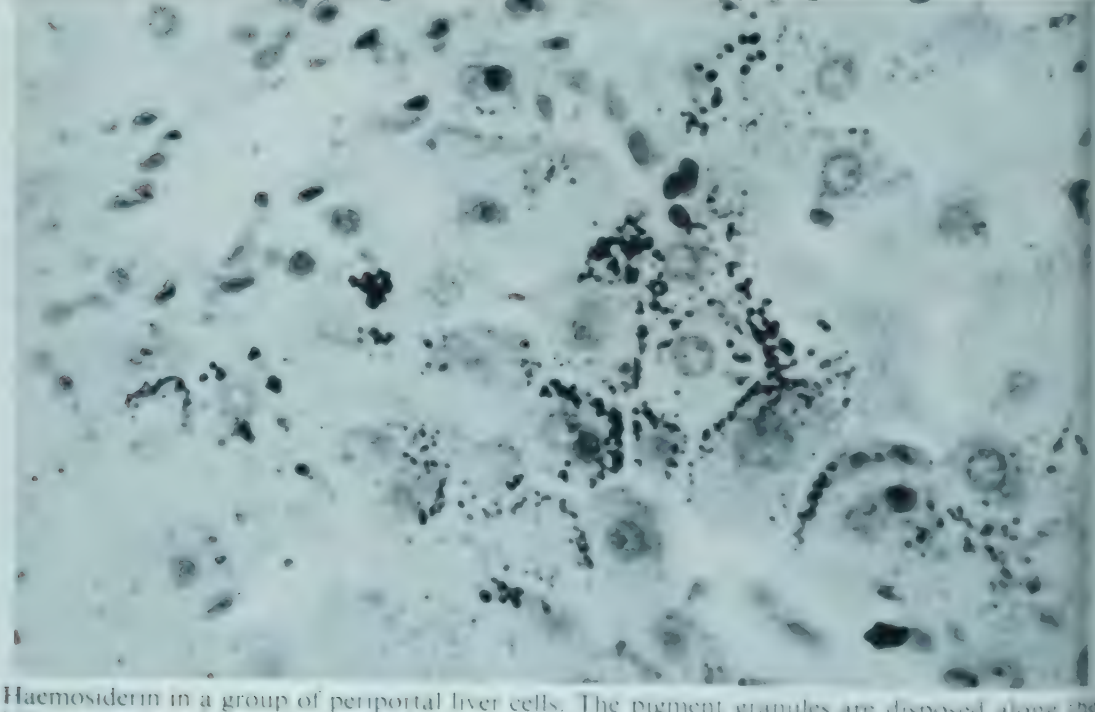
Faintly sudanophil granules in the hepatic cells of the central zones. Subject 19. Sudan III and haematoxylin. (× 430.)

PLATE XLVI

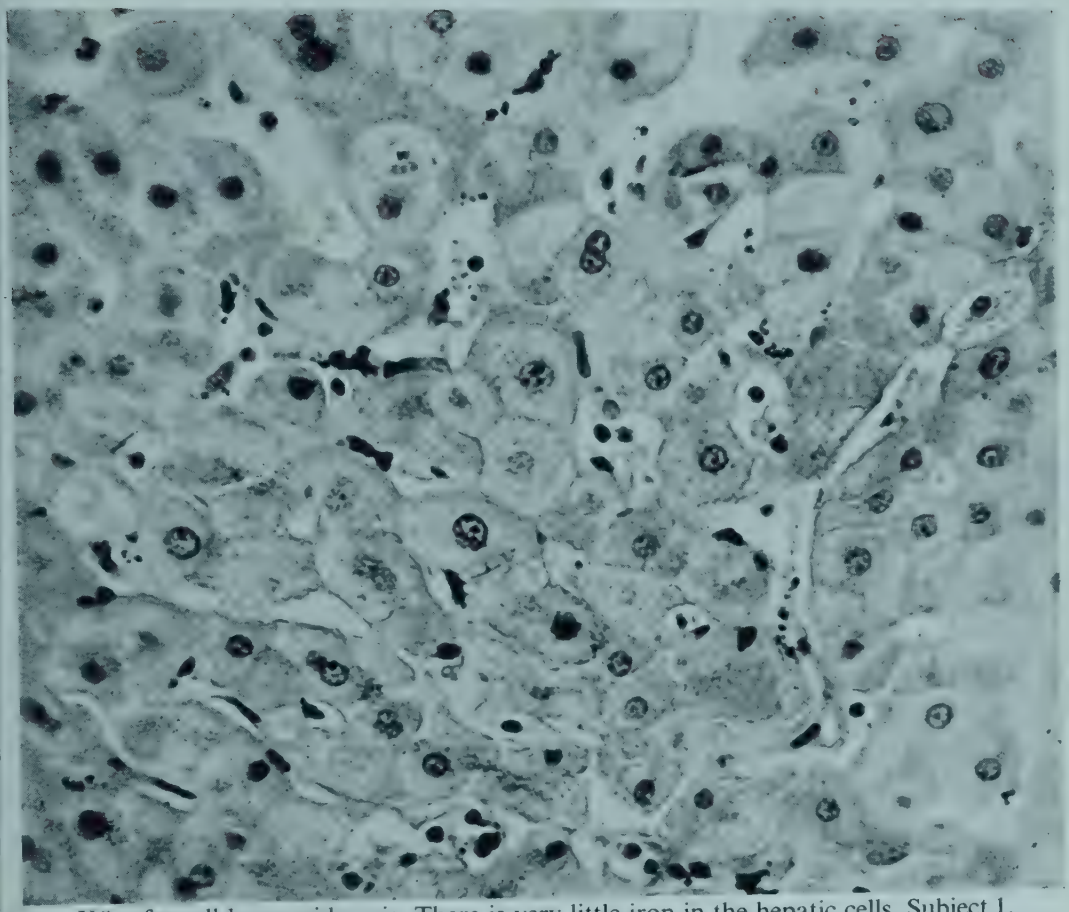


Haemosiderin in the periportal hepatic cells. Subject 10. Ferricyanide and carm alum. (× 150.)

PLATE XLVII

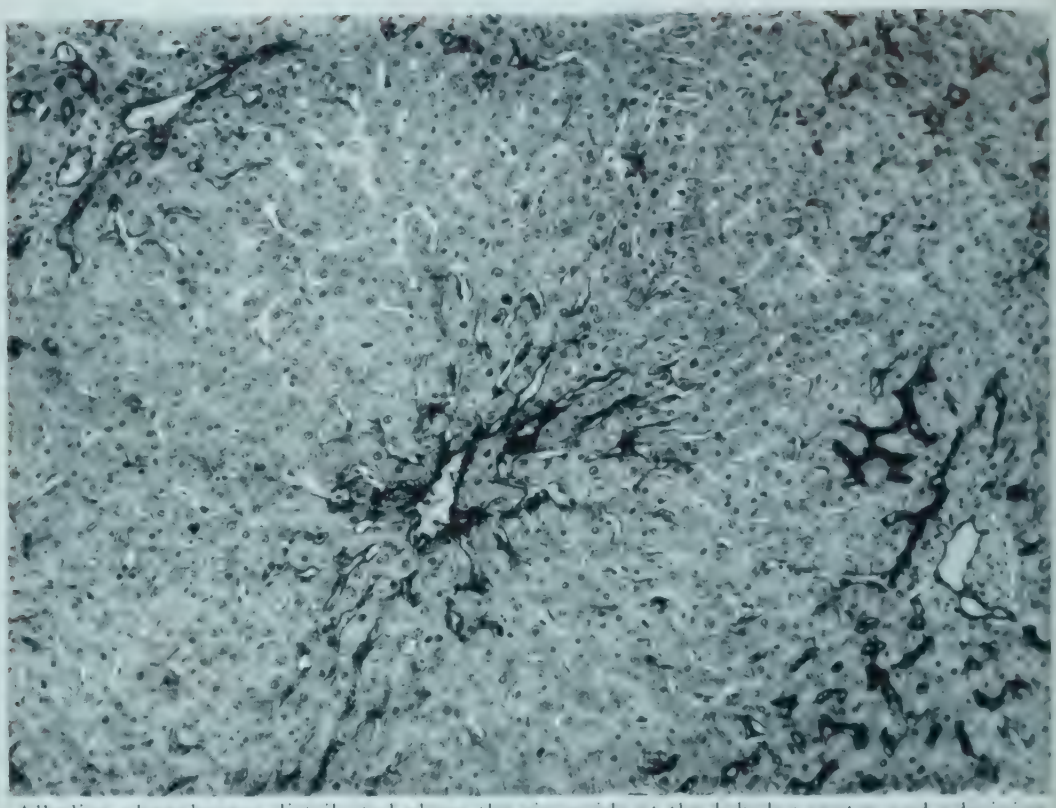


Haemosiderin in a group of periportal liver cells. The pigment granules are disposed along the biliary margins of the cells remote from the sinusoids. Subject 10. Ferricyanide and carm alum. (× 580.)



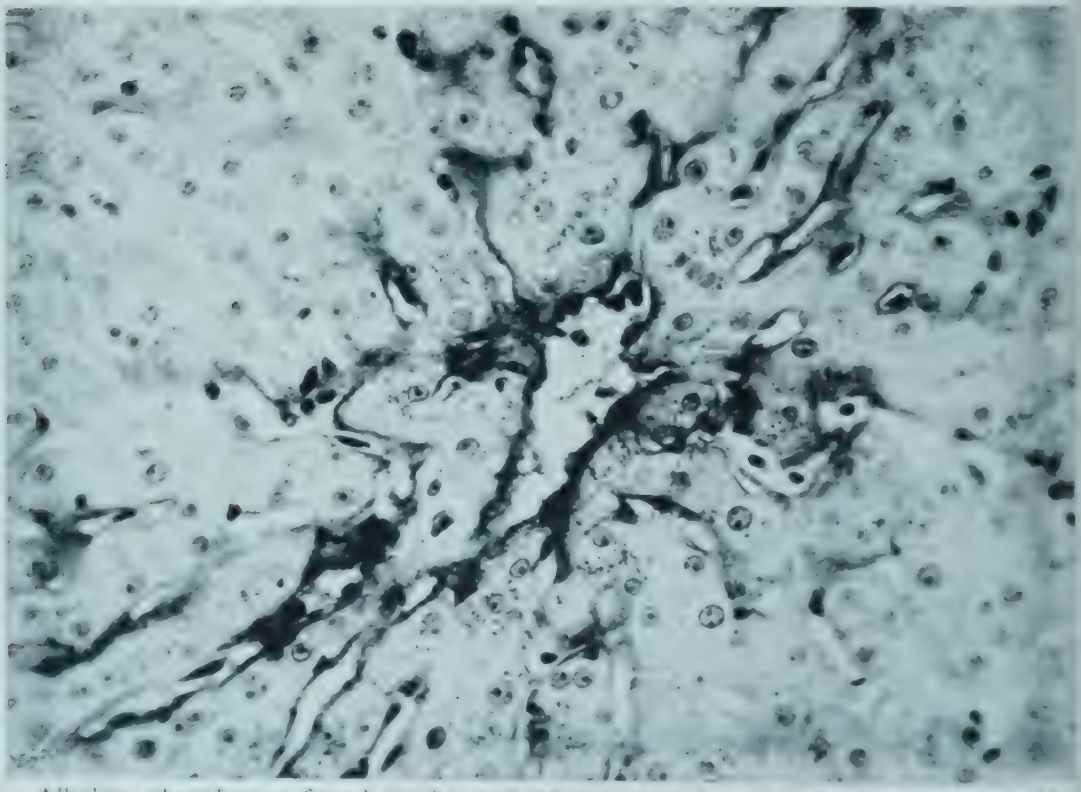
Küppfer cell haemosiderosis. There is very little iron in the hepatic cells. Subject 1. Ferricyanide and carm alum. (× 387.)

PLATE XLIX



Alkaline phosphatase distributed along the sinusoids at the lobular centre and adjoining the portal tracts. Subject 6. Stained Gomori's method. (× 115.)

PLATE L

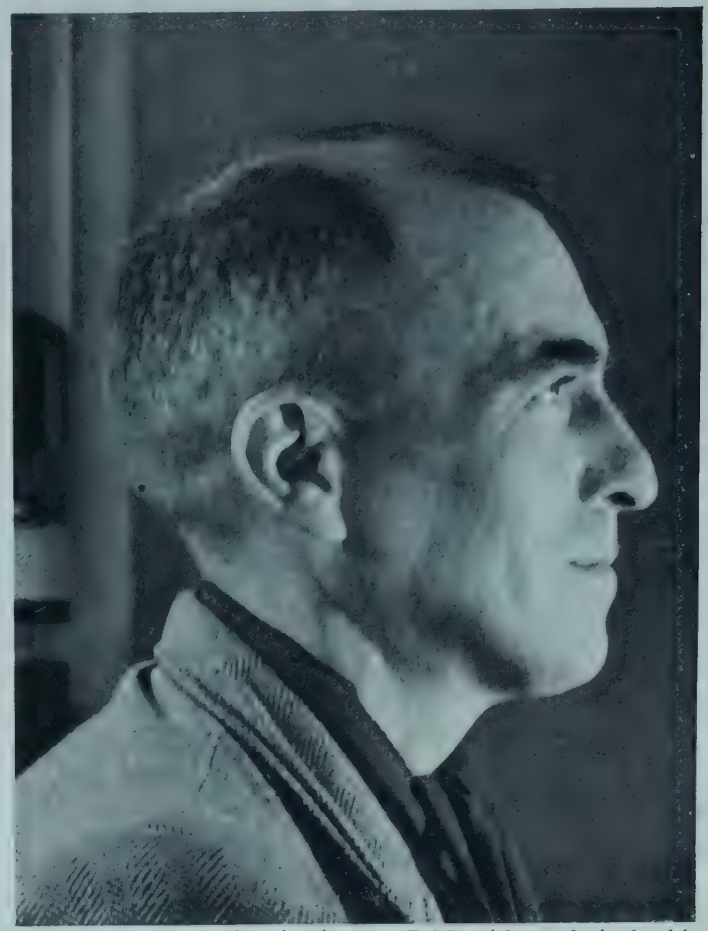


Alkaline phosphatase found in the wall of the central vein and adjoining sinusoids. Granules in the cytoplasm of the liver cells. The nuclear membrane and chromatin network also show the enzyme. Stained Gomori's method. (× 300.)

PLATE LI

Full-face photograph of a repatriated prisoner of war (R 45) with a fat face and swollen parotid glands.

PLATE LII



Profile of a repatriated prisoner (R46) with a relatively thin face. The whole of the enlarged parotid gland is clearly outlined by the shadows thrown on the man's face.

PLATE LIII

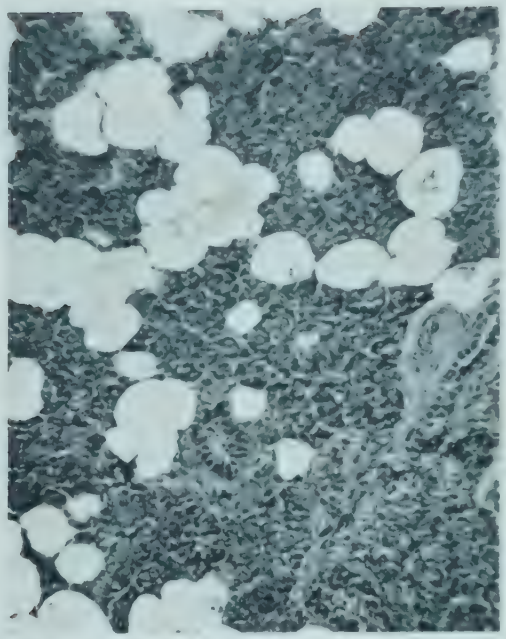


FIG. A. Low-power view of the enlarged parotid gland. (× 110.)

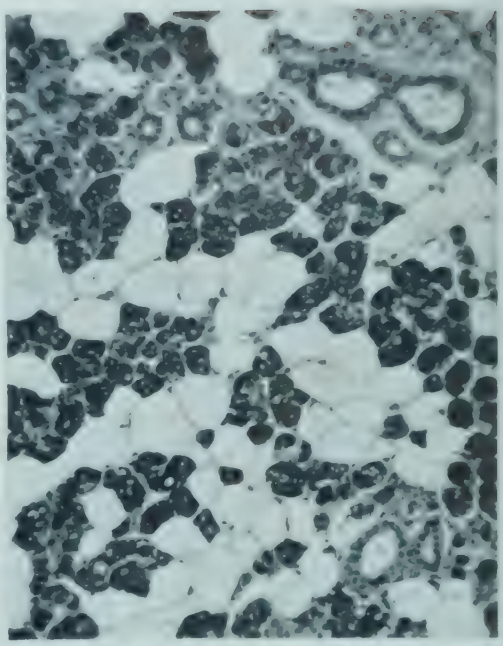


FIG. B. Low-power view of the normal gland from an obese person. (× 110.)

PLATE LIV

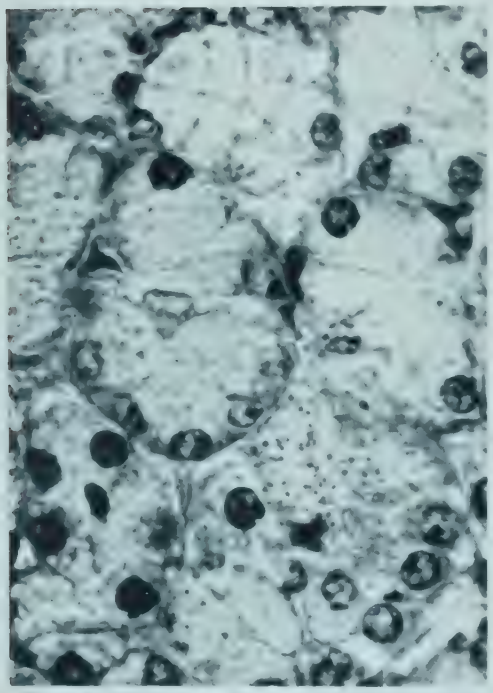


FIG. A. High-power view of typical acini from the enlarged parotid gland. (× 770.)

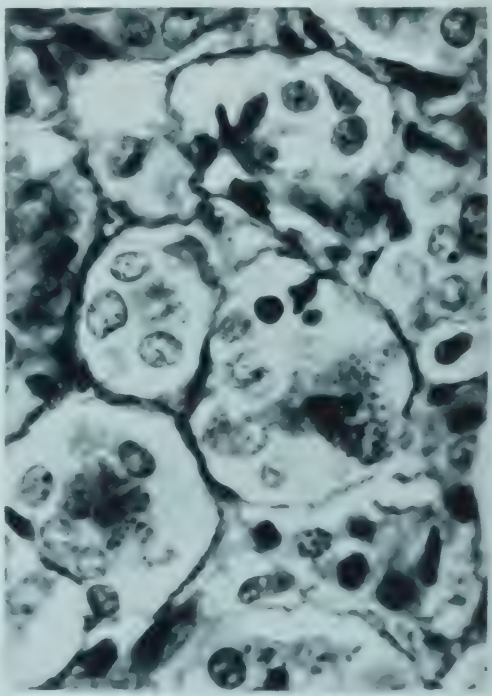


FIG. B. High-power view of typical acini from a normal gland. (× 770.)

PLATE LV

Wilhelm clearing up rubble; Ludwig in background.

PLATE LVI

Emil levelling a bank in the hospital grounds.

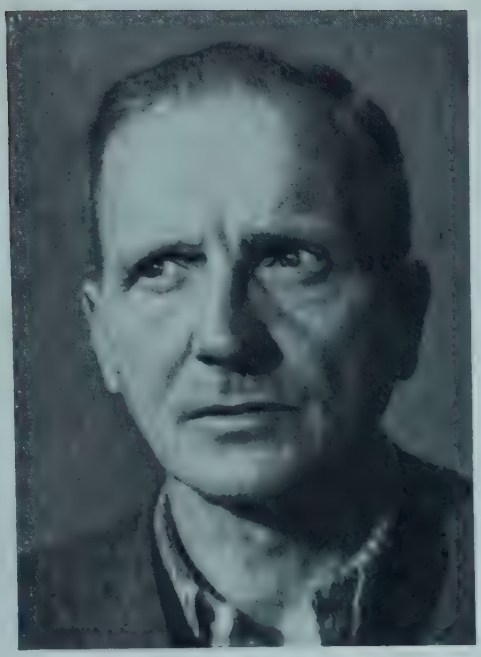
PLATE LVII

Hans at beginning (left) and end of the experiment.

PLATE LVIII

Albert at beginning and end of the experiment.

PLATE LIX

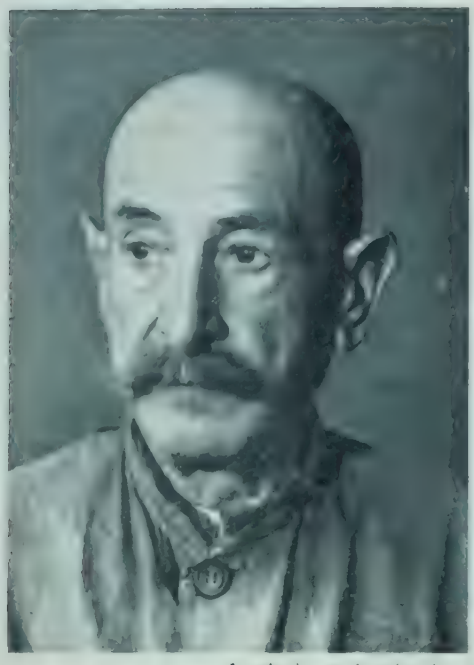


Karl at beginning and end of the experiment.

PLATE LX

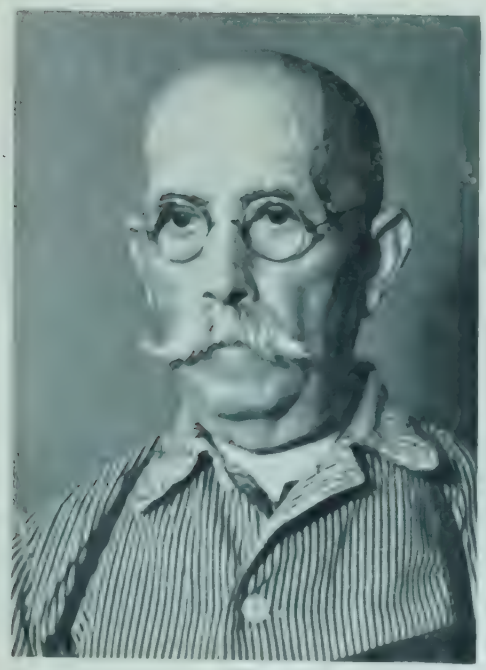
Emil at beginning and end of the experiment.

PLATE LXI



Ludwig at beginning and end of the experiment.

PLATE LXII.



Ewald at beginning and end of the experiment.

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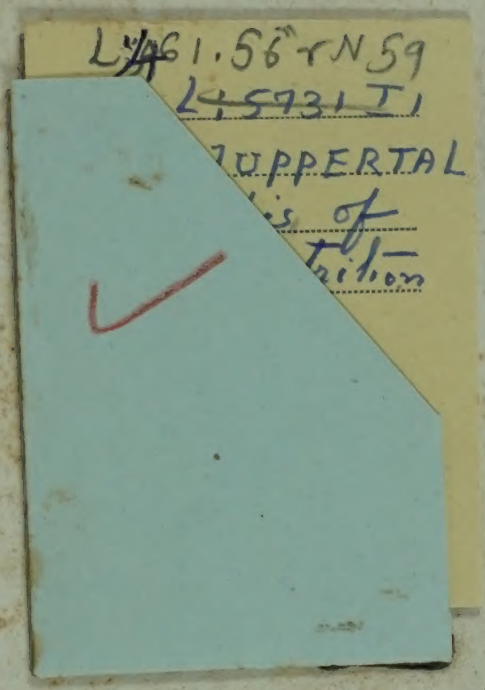
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